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Outpatient rapid optimisation of poorly controlled graves' thyrotoxicosis before surgery - during covid-19 pandemic and beyond: A retrospective study

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Abstract

Purpose: Traditionally, patients with poorly controlled Graves' disease (GD) requiring thyroidectomy would require preoperative admission to control their thyroid function. COVID-19 led to the development and implementation of an outpatient-based protocol for patients unable to tolerate thionamides and/or uncontrolled relapsed disease. We evaluated the safety and efficacy of the outpatient protocol followed by thyroidectomy.

Methods: Patients with poorly controlled GD who underwent thyroidectomy between November 2020-January 2022 were included. Control was achieved with sequential addition and dose-escalation of drugs e.g., Lugol's iodine, cholestyramine, beta-blockers, and steroids (±thionamides) with close out-patient monitoring.

Results: Six patients with a median (range) age of 42.5 (15-47) years underwent rapid optimisation. Pre-protocol median (range) free T4 and free T3 levels at the time of review in surgical clinic were 87.15 (58.8 – 100) pmol/L and 32.7 (21.3 - 50) pmol/L, respectively. Subsequently, free T4 and free T3 levels were significantly reduced ($p=0.028$). None of the patients developed perioperative thyroid storm or long-term postsurgical hypoparathyroidism. There was persistent recurrent laryngeal nerve palsy in one patient.

Conclusions: The outpatient-based protocol was safe, efficient and cost-effective during the pandemic. A close collaboration between medical and surgical teams was key to optimising thyroid function pre-operatively.

Introduction

COVID-19 pandemic represented a global health crisis, affecting many countries worldwide, with over millions of infected subjects and deaths.

Hospitals were overwhelmed by a large number of patients infected with COVID-19 to the point that dedicated wards were created, and healthcare workers were redistributed to work in these new wards. Elective surgery was postponed due to scarce inpatient bed spaces, and operating theatres were considered high-risk areas for transmission of respiratory infections [1]. This environment has encouraged the adoption of strategies to minimise the need for inpatient treatment for a wide range of diseases that are traditionally managed by in-hospital admission.

Graves' disease (GD) is the most common cause of hyperthyroidism accounting for 60-80% of hyperthyroid cases and primarily affecting females aged 40-60 years. This is caused by the production of autoantibodies against thyroid-stimulating hormone receptors. GD is associated with diffuse goitre, ophthalmopathy, dermatopathy, and a rare life-threatening complication known as thyroid storm, a hypermetabolic state causing multiple organ dysfunction [2].

Antithyroid drug (ATD) treatment is the initial standard treatment, usually lasting between 6 and 18 months [3]. Occasionally, definitive treatment, such as surgery or radioiodine ablation (RIA), may be required for relapsed or poorly controlled disease. Total thyroidectomy is preferred in patients who are pregnant, where co-existing thyroid malignancy is suspected, unsuitable for RIA, or those with severe eye disease or large goitre [4]. The primary complications of thyroid surgery are laryngeal nerve injury and hypoparathyroidism, whereas uncommon complications include postoperative bleeding and infection. In preparation for thyroid surgery, the American Thyroid Association guidelines recommend rendering the patient euthyroid and effectively 'beta-blocked' to decrease the risk of intraoperative thyroid crisis [2,5]. Thyroid storm is a rare but severe complication of thyrotoxicosis, with a high mortality rate [6]. The risk of perioperative thyroid storm is reduced by adequate preoperative optimisation with appropriate medical treatment. Different strategies have been proposed to achieve this objective [7,8,9,10,11,12,13]. In patients with uncontrolled GD and those who require urgent surgery, rapid preoperative optimisation of thyroid status can be achieved using thionamides, beta-blockers, and iodine in the form of Lugol's solution [5]. The experience of our centre in the surgical management of both well-controlled and poorly controlled diseases with preoperative management protocols has been previously published [14]. This perioperative optimisation protocol was primarily an 'inpatient' protocol that was modified to facilitate outpatient optimisation for thyroid surgery and called '<Anonymised-hospital> peri-operative protocol in GD' (<Anonymised protocol name>)'' during the COVID-19 pandemic. This study aimed to describe the clinical outcomes of patients undergoing urgent surgery for Graves' disease following rapid optimisation of hyperthyroidism in an outpatient setting.

Methods

Six patients with poorly controlled thyrotoxicosis due to Graves' disease scheduled for total thyroidectomy between November 2020 and Jan 2022 were included (Table 2). The indications for thyroidectomy were poor adherence to or severe side effects of thioamide therapy and at least one of the following criteria:

- Patient's preference to avoid RAI as a definitive treatment
- Relapsed uncontrolled GD needing further medical treatment
- Significant thyroid eye disease
- Very large goitre with compressive symptoms

All patients were advised to attend the outpatient clinic on alternate days for two weeks prior to thyroidectomy for the measurement of thyroid hormone levels and advice on changes to anti-thyroid medications. Trainees in endocrinology (specialist registrars) and specialist endocrine nurses were advised to follow the protocol shown in Table 1. Medications used to control thyroid function included antithyroid drugs (if tolerated) and one or more of the following: propranolol, cholestyramine, and dexamethasone. In addition, all patients were advised to take 0.3 mls Lugol's iodine three times a day for at least ten days prior to surgery. Thyroid function was assessed by measuring free T4 (fT4) and free T3 (fT3) levels. All hormones (fT4, fT3, and cortisol) were quantified using competitive electrochemiluminescence immunoassays (ECLIA, Cobas® 6000 analyser, Roche Diagnostics; reference ranges for fT4 and fT3 were 12−22 pmol/l and 3.1−6.8 pmol/l, respectively. Vitamin D levels in all patients were measured, and vitamin D deficiency was identified. Replacement therapy was initiated before surgery. The patients were reviewed regularly by a senior endocrine trainee doctor to check for intolerance to the medication and encourages patients to adhere to the protocol and maintain compliance. None of the patients required inpatient admission before surgery. Surgery was performed approximately 14 days after starting treatment which was continued up to the day of surgery in all patients. All total thyroidectomies were performed or supervised by one of the two endocrine surgeons at our centre. Patients were admitted for overnight stay and serum calcium and PTH levels were measured on the day after surgery. In addition, all patients underwent voice, wound, and swallowing assessments for postoperative complications. All antithyroid medications were stopped immediately after surgery, except for propranolol which was weaned off for two–14 days in some patients. Oral thyroxine was started at a dose of 1.6 mcg/kg body weight from the morning after surgery. Demographic information, clinical details, use of medications for thyroid optimisation, preoperative thyroid function tests, and postoperative complications were retrospectively collected. Categorical data were reported as frequencies and continuous data as medians with interquartile ranges (IQR). Using IBM SPSS Statistics 28.0, the median values of free thyroid hormones were compared with the corresponding baseline values using the Wilcoxon test. Statistical significance was set at P<0.05. All patient details were accessed only by a member of the clinical team, and identifiable details were anonymised before analyses and reporting. Given the retrospective and observational nature of this study, approval from the regional ethics committee or individual patient consent was not deemed necessary.

Results

Six patients with confirmed Graves' disease (five females and one male with a median age of 42.5 years (range 15−47 years) were included in this study. Two patients developed neutropenia following carbimazole treatment, two patients had poorly controlled relapsed Graves' disease, and two had moderate to severe thyroid eye disease associated with poorly controlled GD. Median (range) fT4 and fT3 levels at the time of review in the surgical clinic were 87.15 (58.8 – 100) pmol/L and 32.7 (21.3 – 50) pmol/L, respectively. In this cohort, all patients received beta-blockers and Lugol's iodine, five were tolerant to thionamides and cholestyramine, and two required dexamethasone.

After 14 days of treatment, the fT4 levels were significantly reduced (p=0.028) to a median (range) of 28.15 (14.6-37.9) pmol/L). Similarly, free T3 levels were significantly reduced (p=0.028) to a median (range) of 7.55 (4.3 to 11.1) pmol/L. These results are shown in figures 1,2,3, and 4. Prior to surgery, all patients had fT3 level below 10 pmol/L. No patients required reoperation for bleeding after surgery, and none developed post-surgical hypoparathyroidism (PoSH). One patient had left recurrent laryngeal nerve damage which was repaired intraoperatively. She was followed up by a Head and Neck Surgeon together with a Speech and Language therapist for voice hoarseness and fluid aspiration. Four months after thyroidectomy, the patient's voice improved and flexible endoscopy of the upper digestive tract showed full glottic closure despite persistent left vocal cord palsy.

Discussion

This report demonstrates that in patients with poorly controlled Graves' disease, rapid optimisation can be effectively achieved in an outpatient setting, without the need for preoperative inpatient treatment. A recent study demonstrated that outcomes following elective surgery for well-controlled disease and urgent surgery after rapid preoperative optimisation of thyroid function tests are similar [14]. The same study described a protocol that helped rapidly optimise 19 patients with poorly controlled Graves' disease before thyroid surgery. Of these 19 patients, 14 (74%) were optimised as inpatients and surgery was performed before the Covid-19 pandemic. Given the scarcity of inpatient beds during the pandemic, a modification of this protocol for outpatient use was adapted for poorly controlled Graves' disease.

The objective of the protocol (Table 1) was to ensure that the patient was clinically euthyroid (heart rate <80 beats/min) with fT4 and fT3 levels under 30 pmol/L and 10 pmol/L, respectively, on the day of surgery. A combination regimen including anti-thyroid drugs, Lugol's solution, beta-blockers, cholestyramine, and dexamethasone was used to safely and rapidly control thyrotoxic patients, as described in previous studies [8-10,15,16,17,12]. In this protocol, rapid preparation was initiated 14 days prior to the planned date for total thyroidectomy.

All patients were advised to continue their current antithyroid medications unless contraindicated, and commenced on Lugol's iodine 0.3 mL three times per day and propranolol 20 mg three times per day ten days prior to surgery. After the protocol was initiated, alternate-day thyroid function tests were performed, and based on the results, other drugs were added as described in the protocol. Five patients continued ATDs treatment throughout the protocol. All patients were started on low-dose propranolol and titrated in response to clinical symptoms and heart rate. The binder cholestyramine was introduced when antithyroid medications did not achieve adequate reduction in ft4 and ft3 a few days after starting the protocol. Ten days before the scheduled date of surgery, Lugol's iodine was initiated with the aim of accelerating the decline in free thyroid hormones. If the target ft3 level was not achieved two days before the surgery, dexamethasone, with a maximum dose of 2 mg twice daily, was considered while on the maximum dose of beta-blockers. Free thyroid hormone levels were measured on alternate days and titrated against the maximum doses of medication stipulated in the regimes. Endocrine doctors in an outpatient setting communicated closely with the surgical team in cases of poor control. Within two weeks of starting therapy, all patients became clinically euthyroid and achieved an fT3 level less than 10 pmol/L.

None of our patients experienced thyroid storm, which can theoretically occur because of an increased availability of free hormones as a result of surgical dissection and more manual handling [6].

We noted a steep decline in the median fT4 and fT3 levels at approximately 6 days (Figures 1 and 2) before surgery which is also supported by a previous report from this unit. It is important to note that it is not necessary to have normal thyroid hormone levels as long as fT4 and fT3 are reduced prior to surgery and the patients are clinically euthyroid [14].

Several studies have reported the use of combining agents to rapidly achieve clinical and biochemical euthyroidism with the goal of limiting perioperative complications.

In our series, thionamides were continued to five patients. Both carbimazole and propylthiouracil (PTU) are known to inhibit thyroid peroxidase which reduces the biosynthesis of thyroid hormones; however, at higher doses, PTU also inhibits the peripheral conversion of ft4 to fT3 [18].

In our case series, dexamethasone was administered twice daily in divided doses of 1-2 mg/day pre-operatively in only two patients nearer to the time of surgery, whereas in two previous case series, dexamethasone was administered to hospitalised patients at higher doses of 2 mg twice daily (4 mg in total) for 10-14 days and continued in the immediate postoperative period [12,17]. Dexamethasone inhibits the peripheral conversion of T4 to T3. Another potential effect of dexamethasone is the suppression of the altered immune response and the subsequent reduction of thyroid gland stimulation [14,16,19].

All our patients were commenced on propranolol to impede the effect of catecholamines secondary to excessive circulating thyroid hormones and to inhibit monodeiodinase type I, which converts T4 to T3 [20]. It was considered safe to taper the drug down over a two-week period after thyroidectomy, as described by other authors [12].

There is compelling evidence for the use of Lugol's iodine, an inorganic iodide composed of iodine and potassium iodide, which decreases the synthesis of thyroid hormones by inhibiting thyroid peroxidase. It also reduces the rate of blood flow and thyroid vascularity, possibly because of its inhibitory effect on vascular endothelial growth factor-A expression, which was demonstrated in cultured human thyroid follicles [21-23]. Therefore, Lugol's iodine reduces intraoperative bleeding and allows better visualisation and preservation of the surrounding nerves, vasculature, and parathyroid glands. However, some authors have questioned the value of these benefits [24]. Langley et al compared the different therapies used in the literature for a favourable outcome during total thyroidectomy but could not conclude that the use of inorganic iodine added any benefits at surgery in those patients already on different modalities of treatment to control thyrotoxicosis pre-operatively [13].

Cholestyramine is an ion-exchange resin that interferes with endogenous thyroid hormone absorption via enterohepatic circulation [25,26]. Other drugs such as lithium which is concentrated by follicular cells, inhibit thyroidal iodine uptake and iodotyrosine coupling, alter thyroglobulin structure, and inhibit thyroid hormone release into the circulation. However, it has a narrow therapeutic range and has been used extensively because of the risk of toxicity [27]. Amiodarone contains a high iodine content that can acutely block thyroid synthesis, which can be used to achieve rapid clinical euthyroidism, as reported in a letter to the Editor by Mooij et al. [28]; however, this was limited to a case study. Therapeutic plasmapheresis is a treatment modality that requires trained medical staff, is invasive, and is associated with a high risk of serious complications. It should be reserved only for refractory or emergency cases. It has been reported to be effective for the rapid control of thyrotoxicosis prior to RIA [29].

Limitations

Our study had several limitations. First, this study included only a small number of patients. However, most patients with Graves' disease achieve good control of thyroid function before thyroidectomy. No control groups were included. However, in a retrospective cohort study, rapid optimisation was performed in poorly controlled patients, with a cohort of well-controlled patients undergoing surgery. The added value of this report is to demonstrate that outpatient optimisation is effective. Alternative regimens may also equally effective in ensuring this objective and this has not been assessed in this report. The specific indications of surgery were varied and the definition of 'poorly controlled' Graves' disease can be considered to be subjective and not standardised.

Conclusion

In conclusion, our report shows that effective and rapid preoperative preparation of patients with Graves' disease is achievable with a treatment regimen initiated and maintained in an ambulatory (outpatient) setting. Use of this regimen may help reduce the need for in-hospital treatment and reduce the financial burden of inpatient admissions.

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