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Review

Beta-blockers and the thyrotoxic patient for thyroid and non-thyroid surgery: a clinical review

Tay S[1]*, Khoo E[1], Tancharoen C[2], Lee I[3]

Abstract

Introduction

Thyrotoxic patients presenting for surgery should ideally be biochemically and clinically euthyroid. This is conventionally achieved through the use of anti-thyroid drugs, beta-blocker therapy and iodine. However, there are some circumstances where anti-thyroid drugs may not be a viable option. The implications of this scenario are not widely reported in the literature. This clinical review looks at the evidence on the safety of beta-blocker therapy without the use of anti-thyroid drugs in the preparation of the thyrotoxic patient for surgery. We also highlight key points in the pathophysiology of thyrotoxicosis and the management goals of these patients.

Conclusion

In circumstances where the use of anti-thyroid drugs is not possible in the preoperative management of patients for thyroid or non-thyroid surgery, the use of beta-blockers has been shown to be safe and effective. Safety can be increased by using iodine with or without corticosteroids up to the day of surgery in the rapid preoperative preparation of a severely thyrotoxic patient.

Introduction

A thyrotoxic patient undergoing surgery should ideally be rendered biochemically and clinically euthyroid prior to surgery[1]. This is through a combination of anti-thyroid drugs (ATD) and beta-blockers. However, in some circumstances, patients can be adequately managed with beta-blockers and potassium iodide[1]. The question remains though, how safe is this therapy compared with the conventional use of ATDs and beta-blockers? There have been several studies in the past that have suggested a role for sole beta-blocker therapy in the preoperative management of thyrotoxic patients. This paper aims to review the current literature to evaluate the safety of this practice.

Discussion

Thyrotoxicosis is a hypermetabolic syndrome secondary to elevated levels of thyroid hormones. The most common causes of thyrotoxicosis are Graves' disease, toxic multinodular goitre and toxic adenoma[1,2]. These diseases cause hyperthyroidism or an increase in both the synthesis and secretion of thyroid hormones by the thyroid. Other causes of thyrotoxicosis include thyroiditis or iatrogenesis. These causes do not increase the synthesis of thyroid hormones, and the use of ATDs is therefore contraindicated.

The symptoms of thyrotoxicosis are due to an excess of beta-adrenergic activity, and include hyperactivity, nervousness, tremor, weight loss and sweating[3–6]. Relevant to anaesthesia, an excess of thyroid hormones can affect cardiovascular physiology as shown in Figure 1. Importantly, these cardiovascular effects predispose a patient to develop supraventricular arrhythmias. In patients with pre-existing cardiac disease, ischaemia or failure may be precipitated[7]. Thyroid storm is a life-threatening complication of uncontrolled and severe thyrotoxicosis that can be triggered by various insults such as surgery, anaesthesia, manipulation of the thyroid or sepsis. It carries a high mortality rate of 10%–30%[8,9]. Its incidence, however, is rare due to the widespread use of ATDs and beta-blockers[1–6,9].

Patients presenting for surgery with thyrotoxicosis can be divided into those requiring emergent care unrelated to thyroid, or those that are thyroid-related. The indications for thyroid-related surgery are

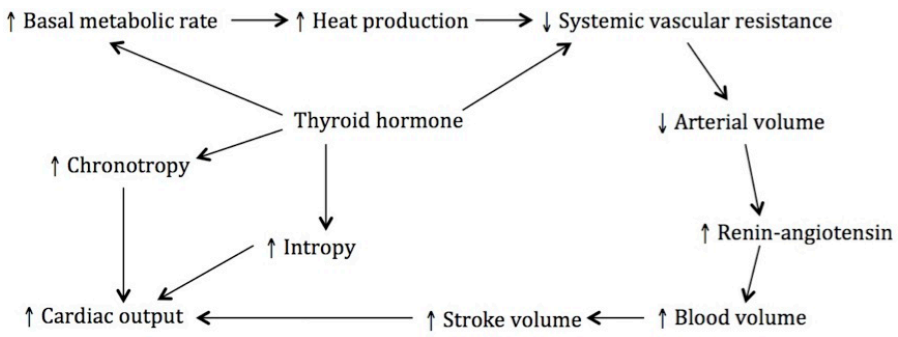

Figure 1: Effect of thyroid hormones on cardiovascular physiology (Adapted from Klein et al. 2001)[7].

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summarized in Table 1[1,10]. There are currently three major forms of treatment: medical therapy (ATD),[131]I and surgery[1,11]. All are safe and equally as successful when comparing long-term quality of life[12], but each with their own advantages and disadvantages. Choice of treatment must take into account numerous factors—patient age, sex, desire to have children, underlying comorbidities and the personal "philosophies" of both the patient and physician or surgeon[13].

Table 1 Indications for thyroid-related surgery
Rapid correction of thyrotoxic state
Failure, adverse side effects or non-compliance of medical therapy
Avoidance of exposure to radioactivity to ^{131}I (children or pregnant/breast-feeding women)
Large goitre (>80 g)
Children <5 year of age
Moderate to severe or sight threatening Graves' ophthalmopathy
Presence of symptoms or signs of compression within the neck
Substernal or retrosternal extension of thyroid
Potential for coexisting thyroid cancer
Coexisting hyperparathyroidism
Thyroid-stimulating hormone producing pituitary tumours
Patient preference

Current preoperative preparation of a thyrotoxic patient

Preoperative optimization of the thyrotoxic patient depends on its aetiology. Targets for action are pathways in thyroid hormone synthesis, secretion and its peripheral action[1,14,15]. The aim is to reduce the risk of perioperative thyroid storm. For thyrotoxic patients secondary to hyperthyroidism (not thyroiditis or iatrogenesis), elective surgery should be postponed for 3–6 weeks so that a euthyroid state can be achieved with an ATD and beta-blockers as indicated for symptomatic relief and cardioprotection[1,2,16]. With emergent surgery, there is insufficient time to allow ATDs to achieve euthyroid state. Therefore, a combination of beta-blockers, iodine and high-dose steroids is given to rapidly facilitate safe surgery.

Thionamides are a class of ATD that include propylthiouracil (PTU), carbimazole and its active metabolite methimazole[15]. They act by halting thyroid hormone synthesis by blocking organification of iodine and coupling of iodotyrosines. PTU additionally inhibits peripheral deiodination of thyroxine (T_4) to triiodotyrosine (T_3)[6,15]. Carbimazole or methimazole, however, are generally preferred as they have the benefit of once-a-day administration and reduced side effects compared to PTU[1]. The exception is during the first trimester of pregnancy where PTU is not considered to be teratogenic[1]. Rare side effects include agranulocytosis and hepatotoxicity[1,5,17]. Common side effects include fever, arthralgia, rash and urticaria [1,5,17]. Since ATDs have no effect on the release of preformed thyroid hormones, it takes several weeks of therapy to render a patient euthryoid[5,16,17]. This regimen, however, has been reported to result in a larger, more vascular and friable gland due to thyrotropin (TSH) stimulation of the thyroid in response to ATD-induced hypothyroidism[15,13]. This unwanted effect can be lessened by increasing the duration of treatment[13,18] or through the use of iodine[1].

In supra-physiological doses, Lugol's iodine inhibits thyroid hormone synthesis via the Wolff–Chaikov effect, and the release of preformed hormones[3,15]. The anti-thyroid effects are seen within the first 24 hours and maximally at 10 days of therapy[15,19]. Iodine has also been reported to reduce vascularity and friability of the thyroid gland, thereby possibly lowering surgical bleeding risk[19,20]. Oral iodinated radiographic contrast agents such as ipodate and iopanoic acid can also be used. It has the additional beneficial effect of reducing peripheral conversion of T_4 to T_3[15]. Unfortunately, these agents are not available in many countries[1]. Use of iodine should be restricted in the preoperative period for no longer than 10 days. This is because of an "escape phenomenon" where an excess of iodine incorporates into new thyroid hormones, leading to a secondary rise in thyroid hormones and worsening of the thyrotoxic state. This occurs after 10–14 days of therapy[15,21,22].

Several clinical features of thyrotoxicosis are due to sympathetic-mediated stimulation relating to increased beta-adrenoreceptor up-regulation and sensitization to catecholamines[3,15,23]. Since the 1960s, propranolol has been the agent of choice to attenuate the heightened beta-adrenoreceptor-mediated effects of thyrotoxicosis[2,24,25]. Other beta-blockers have become available since then, including more beta-1 selective agents (metoprolol), long-acting agents (atenolol) and very short-acting agents (esmolol). Each has their own advantages and disadvantages in managing a thyrotoxic patient. However, the main limitation with all beta-blockers is that they do not alter the underlying hypermetabolic state. Therefore, long-term sole beta-blocker therapy is not recommended[15,26].

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Finally, high doses of dexamethasone, hydrocortisone or betamethasone are used as adjunct therapy when a severely thyrotoxic patient needs to be rapidly prepared for surgery[27]. They inhibit secretion of thyroid hormone and peripheral conversion of T_4 to T_3[3,17,28].

Safety of beta-blockers as sole therapy

The use of ATDs may not be possible in patients undergoing emergency surgery, non-compliant patients and patients that are refractory to ATDs[16,29,30]. In view of the established safety of conventionally prepared thyrotoxic patients for surgery, it is essential that any deviation from this is comparably safe and effective[31].

During the 1970s to the mid-1990s, numerous studies were performed with results advocating the use of beta-blockers, in particular propranolol, alone or in combination with iodine in the preoperative treatment and stabilization of the thyrotoxic patient. These results are summarized in Table 2[31–45]. They show that this regime can safely provide rapid control of the peripheral manifestations of hyperthyroidism, producing a clinically euthyroid patient in a relatively short period of time.

Given that beta-blockers do not interfere with the release of thyroid hormone, the fear remains that a clinically euthyroid patient treated with beta-blockers only remains exposed to high levels of circulating thyroid hormone. This then increases the risk of perioperative thyroid storm. It has been reported that the incidence of post-operative hyperthyroid symptoms occurs in 5%–20% of patients prepared with beta-blocker therapy alone[13,40–44]. Many of these cases may be attributed to the short half-life of propranolol and the need for regular administration. Therefore, close supervision is required, especially in the first 24 hours post-surgery. Also, instead of weaning beta-blockers immediately after surgery like one would do if a patient were conventionally prepared with ATDs, they should be continued for 5–7 days post-operatively to prevent hyperthyroid symptoms and avert the risk of thyroid storm. This is because the biological half-lives of the excess circulating T_3 is 1–2 days and T_4 is 3–4 days in hyperthyroidism[46].

There have been several small retrospective case series which have reported the occurrence of thyroid crisis in patients undergoing surgery following sole preparation with propranolol[24,45,47–50]. This is in contrast to the prospective studies shown in Table 2. The circumstances in which thyroid storm occurred were either the dosage of propranolol being too low (160 mg/day or less) or the response to beta-blocker therapy not

Table 2 Six hundred and eighty thyrotoxic patients for thyroidectomy prepared with beta-blockers ± iodine only (Adapted from Lee et al. 1982)[21]

Author	Year	No. of patients	Beta-blocker	Iodine	Surgery	Storm	Results	Country
Lee et al.[32]	1973	20	Propanolol	No	Yes	No	Good	USA
Michie et al.[33]	1974	37	Propanolol	No	Yes	No	Good	Scotland
Michie[34]	1975	47	Propanolol	No	Yes	No	Good	England
Toft et al.[35]	1976	40	Propanolol	No	Yes	No	Good	Scotland
Caswell et al.[36]	1978	24	Propanolol	No	Yes	No	Good	USA
Anderberg et al.[37]	1979	38	Propanolol	No	Yes	No	Good	Sweden
Tevaarwerk et al.[38]	1979	20	Propanolol	No	Yes	No	Good	Canada
Malliere et al.[39]	1980	5	Propanolol	No	Yes	No	Good	France
Feek et al.[22]	1980	10	Propanolol	Yes	Yes	No	Good	Scotland
Feely et al.[40]	1981	44	Propanolol	No	Yes	No	Good	England
Lee et al.[21]	1982	140	Propanolol	No	Yes	No	Good	France
Peden et al.[41]	1982	17	Nadolol	Yes	Yes	No	Good	Scotland
Lennquist et al.[42]	1985	93	Propanolol	No	Yes	No	Good	Sweden
Gerst et al.[26]	1986	12	Atenolol/Nadolol	No	Yes	No	Good	USA
Adlerberth et al.[43]	1987	15	Metoprolol	No	Yes	No	Good	Sweden
Vickers et al[44]	1990	95	Propanolol	No	Yes	No	Good	India
Hermann et al.[45]	1994	23	Propanolol	No	Yes	No	Good	Austria

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being adequately assessed prior to the commencement of surgery. This is important as there is large individual variability in response to propranolol[40,41,51]. Therefore, targets of heart rates <90 beats per minute and absence of symptomatic thyrotoxicosis should be used as end points prior to proceeding to surgery.

A biochemically euthyroid state is generally considered mandatory prior to surgery because of the concern that surgical manipulation of the hyperactive tissue may precipitate the release of thyroid hormone into the circulation giving rise to a thyroid storm[44]. Hermann et al. in 1994 reported a study of 23 patients with severe hyperthyroidism (defined as free T_3 or T_4 levels at least 300% the maximum normal value) prepared with propranolol alone[44]. Hormone levels were measured perioperatively—including from the middle thyroid vein before and after surgical manipulation of the gland, and from the cubital vein after removal of the thyroid lobes. There were no episodes of thyroid storm, and levels of free T_4 and T_3 were not shown to change with the manipulation of the gland. These findings raise the possibility that biochemical euthyroidism may not be an absolute prerequisite for thyroidectomy.

Use of beta-blockers is also associated with reduced thyroid gland vascularity, allowing for safe mobilization and resection of the gland by the surgeon. This minimizes the risk of excessive blood loss and damage to nerves or parathyroid glands[18,40–43]. On the contrary, studies by Lennquist in 1985[42] and Adlerberth in 1987[43] reported no difference in the consistency and vascularity of thyroids prepared with beta-blockers compared with those prepared with ATD. Importantly, they also documented no significant difference in post-operative complications of haemorrhage, hypocalcaemia or recurrent laryngeal nerve injury between the two groups.

Clinical evidence for specific beta-blockers

Propranolol is the most commonly used beta-blocker to treat thyrotoxicosis and has been the mainstay beta-blocker therapy to prepare thyrotoxic patients for surgery[21,22,32–40,42,44,45]. An advantage of propranolol compared to other beta-blockers is that it blocks peripheral conversion of T_4 to T_3 at high doses. Intravenous propranolol can also be given in the event oral intake is limited post-operatively[39]. A disadvantage is its short half-life requiring high doses and frequent administration of up to four times daily to maintain therapeutic plasma levels. This can limit medication compliance and increases the risk of perioperative thyroid storm or hyperthyroid symptoms if doses are missed or inadequate doses are prescribed[10]. It also has a wide inter-individual variation range[40]. Being a non-selective beta-blocker, it is contraindicated in patients with reversible obstructive airways disease[4].

Difficulties surrounding the use of propranolol led to a number of studies of other beta-blockers, in particular, more cardioselective agents such as metoprolol[4]. In a double-blind crossover trial by Murchison in 1979,[51] each patient received 4 weeks of treatment with propranolol and 4 weeks with metoprolol. All showed improvement in clinical symptoms and signs. These results suggest that metoprolol is as effective as propranolol. Furthermore, there is also a stronger association between plasma metoprolol levels and clinical efficacy than with propranolol. These findings are supported by Adlerberth 1987[43] and Vickers in 1990.[44] Metoprolol also offers a simpler twice-daily dosing regimen and can be given intravenously when oral administration is limited.

Nadolol and atenolol, long-acting beta-blockers, have also been suggested as possible alternatives to propranolol[26,41]. Peden in 1982[41] reported the use of daily nadolol and lugol's iodine in 17 thyrotoxic patients undergoing subtotal thyroidectomy. All patients were clinically euthyroid by the time of surgery with no episodes of thyroid storm or exaggeration of the thyrotoxic state post-operatively. Similarly, Gerst in 1986[26] studied 12 patients prepared with either nadolol or atenolol without iodine. No intolerance or side effects to these medications were noted, and surgery was performed without complication. While the use of these long-acting beta-blockers is less studied than propranolol, existing evidence demonstrates their safety and efficacy in the preparation of the hyperthyroid patient for surgery.

Esmolol is a very short-acting cardioselective beta-blocker that is given as a continuous intravenous infusion[52]. It is used primarily in the intensive care setting to treat severe and uncontrolled thyrotoxicosis, and also to control haemodynamics intra-operatively[1]. Compared with other beta-blockers, this agent has a faster onset and offset of action and is much easier to titrate due to its short half-life. This is advantageous in controlling severe thyrotoxicosis or storm, which are dynamic clinical situations[1].

Conclusion

In circumstances where the use of ATDs is not possible in the preoperative management of patient presenting for thyroid or non-thyroid surgery, the use of beta-blockers has been shown to be safe and effective. However, to increase safety, we recommend the use of iodine with or without corticosteroids up to the day of surgery in the rapid preoperative preparation of the severely thyrotoxic patient. This should not be continued for longer than 10 days. The choice of beta-blocker is clinician-dependent and should be titrated to ideally achieve a heart rate of <90 beats per minute and the absence of symptomatic thyrotoxicosis prior to proceeding to surgery. If this

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is not possible, then patients should be managed in an intensive care setting utilizing an esmolol infusion. Post-operatively, patients should be managed in a high-dependency care setting to provide close supervision during the first 24 hours. Beta-blocker therapy should also be continued for 5–7 days with its dose titrated to the patient's heart rate.

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