

THE USE OF CARBIMAZOLE AND ESMOLOL IN THE TREATMENT OF THYROTOXICOSIS (GRAVE'S DISEASE) BY SUB-TOTAL THYROIDECTOMY IN NORTHERN GHANA

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ABSTRACT

For decades, the preparation of a hyperthyroid patient for surgery took several weeks or months utilizing thyroid blocking agents and iodine [24, 25]. Since the 1960s, propranolol has been the agent of choice to attenuate the heightened β - blocker effects of thyrotoxicosis[25]; also in 1973, a preliminary report of 20 patients with hyperthyroidism treated with propranolol and thyroidectomy was presented [25, 31]. It was found that thyrotoxic patients could be prepared for surgery within 24 hours with oral or intravenous propranolol. Propranolol (non-selective β -blocker) effectively neutralizes the symptoms of autonomic hyperactivity including sweating, tremors, fever, tachycardia, hypertension, arrhythmias, dilatation of blood vessels, increased pulse rate and resultant heart failure [11, 12, 13, 25], which significantly affect the thyroid function; this also results in reduced incidence of post-operative hypothyroidism, recurrent laryngeal nerve damage or post-operative hypo-parathyroidism [32]. Esmolol is a newer cardio-selective β_1 -blocker [1, 30]. The beneficial effects of esmolol over propranolol is its cardio selective β_1 -receptor blocker property and its rapid onset ability [1, 24]. Esmolol also has a very short duration of action and no significant intrinsic sympathomimetic or membrane stability activity at therapeutic dosages. It is a class-2 antiarrhythmic drug; decreases the force and rate of heart contractions by blocking β_1 -adrenergic receptors in the heart and other body organs. Esmolol also prevents the actions of adrenaline and non-adrenaline in the body. It is therefore used in surgery (during induction and endotracheal intubation, perioperative and postoperative periods) to prevent or treat tachycardia, hypertension, acute supraventricular tachycardia or aorta dissection [1, 2, 3, 4, 24]; it suppresses the manifestations of Grave's disease related increased sympathetic activity. Grave's disease is said to be the most common cause of hyperthyroidism (80-90%) [9]. Literature shows the newer cardio-selective agents such as esmolol is thought to be a "jack of all trades" among drugs used in anaesthesia because it prevents and treats cardiovascular responses due to perioperative stimuli. In addition to its effects on the sympathetic nervous system, esmolol also influences core components of an anaesthetic regimen such as analgesia, hypnosis and memory function [2-5]. Antithyroid drugs are one of the treatment options for Grave's disease [24,28 ,30]. Carbimazole, an antithyroid drug is said to be widely used as the drug of choice in thyrotoxicosis (Grave's disease) except in pregnancy [8]. This study sought to investigate and evaluate the effects of carbimazole and esmolol combination in the management of thyrotoxicosis by sub- total thyroidectomy in Northern Ghana from 2011 to 2013 at Tania Specialist Hospital, Tamale. To the best of our knowledge, no such study has been done in the past. Bilateral sub-total thyroidectomy was performed on 20 patients with thyrotoxicosis in whom tablet carbimazole was administered 7 to 10 days pre- operatively. Intra- operatively esmolol was also given. Then post- operatively, carbimazole was again given for a period of 5 to 10 days to prevent cardiac complications, before, during and after surgery. Transient complications, intra- and post-operatively were monitored and observed for, including hypoparathyroidism, bleeding or haematoma, wound infection, tracheal collapse, recurrent laryngeal nerve damage, but none was detected in all cases. Thyroid function tests (TSH, T₃, T₄)

levels returned to normal levels in all cases within the post-operative period from two (2) to four (4) weeks.

Conclusion: This study recommends bilateral sub-total thyroidectomy for Grave's disease (thyrotoxicosis) in patients managed with carbimazole and esmolol combination. This has advantages over the conventional use of carbimazole and potassium iodide combination for same indication.

Keywords: Carbimazole, Esmolol, Thyrotoxicosis/Grave's Disease, Sub-total thyroidectomy, Northern Ghana.

INTRODUCTION

Grave's disease (toxic diffuse goitre) is an autoimmune disease frequently causing enlargement and over functioning of the thyroid gland, hyperthyroidism in 80-90% of cases [9]. Grave's disease affects up to 2% of the female population, sometimes after childbirth and occurs seven (7) to eight (8) times more often in females than in males [16]. Most often it is also seen in middle age patients 30 to 50 years, but not uncommon in adolescents, during pregnancy or during menopause or people more than 50 years [16].

Diagnosis is made based on clinical findings although thyroid hormone tests may be useful as well as sonography and CT- scanning of the thyroid gland, chest radiography and laryngoscopy. Signs and symptoms of the disease commonly includes, insomnia, hand tremors, hyperactivity, hair loss, excessive sweating, heat intolerance, weight loss despite increased appetite, diarrhoea, palpitations, muscle weakness, skin warmth and moisture, exophthalmos, goitre and pre-tibial myxoedema [11, 12, 13]. Grave's disease occurs when thyroid stimulating immunoglobulin's recognise and bind to the thyrotropin receptor (TSH receptor). It mimics the TSH to that receptor and activates the secretion of T₄ and T₃ and the actual TSH level will decrease in the plasma. The TSH level falls because the Hypothalamus-Pituitary-Thyroid negative feedback loop is working. The result is very high levels of circulating thyroid hormones and the negative feedback regulation will not work for the thyroid gland.

The management of the Grave's disease includes the use of anti-thyroid drugs, radioactive iodine (I-131) and thyroidectomy [9, 24]; but operating on a frankly hyperthyroid patient is dangerous. Prior to thyroidectomy preoperative treatment is given to render the patient "euthyroid" [24]. Radioactive-iodine, is now the treatment of choice by most endocrinologists. However antithyroid drugs are used in younger patients, pregnant and lactating patients [9]. Surgery is recommended for patients with large goitre exerting pressure on the trachea and/or oesophagus or suspicion of cancer or a retrosternal goitre or patients with imminent cardiac complications or ophthalmopathy, by employing either sub-total thyroidectomy or Hartley-Dunhill procedure (Hemi- thyroidectomy on one side and partial lobectomy on the other side). Surgery for thyrotoxicosis is rapid and permanent, highly safe and successful and has an important and complimentary role with modern therapy.

Carbimazole is widely used to treat hyperthyroidism [8]. It is converted to the active form, methimazole. Methimazole prevents the thyroid peroxidase enzyme from coupling and iodinating the tyrosine residues on thyroglobulin, hence reducing the production of T₃ and T₄ [28,]. Literature states therapy for hyperthyroidism generally starts with a high daily dose 15 to 40 mg of carbimazole continued until the patient has normal thyroid function, and then carbimazole is

reduced to a maintenance dose of 5 to 15 mg daily. The treatment is usually given for 12 to 18 months followed by a trial withdrawal [13]. Literature also states that the onset of anti-thyroid effect of carbimazole is rapid but the onset of clinical effects on thyroid hormone levels in the blood is much slower. This is because the large store of pre-formed T₃ and T₄ in the thyroid gland and bound to thyroid binding globulin (99% bound) has to be depleted before any beneficial clinical effect occurs [27, 28].

Tachycardia is a characteristic feature of thyrotoxicosis at all ages [17, 18], but the older the patient, the more frequent the occurrence of atrial fibrillation [10]. Treatment of thyrotoxicosis is followed by slowing the heart rate so that more than half the patients do not develop atrial fibrillation. Drug therapy combined with surgery or with radioactive iodine therapy, tachycardia usually reverts to sinus rhythm [23]. Circulatory features of thyrotoxicosis crisis or storm, exists when tachycardia due to thyrotoxicosis is associated with hyperpyrexia, diarrhoea, psychiatric disturbance, muscle weakness and profuse sweating; with thyroid storm cases, urgent control of the tachycardia, cardiac arrhythmias and hyper-metabolic state is required to avert any cardiac arrest or cardiac failure developing [28,29]. Thyroid storm is a life threatening condition, with mortality rate of 10-30% [28, 29]. In such situations, blockage of the sympathetic nervous system or depletion of tissue stores of catecholamines may be of urgent importance [24, 26].

Methods/Results

20 thyrotoxic patients were prepared for bilateral sub-total thyroidectomy with tablet carbimazole 40mg daily pre-operatively for 7 to 10 days. The sudden rise of pulse rate intra-operatively was then managed with intravenous esmolol 1mg/kg bolus over 30 seconds followed by 150-300mg/kg/minute infusion. From the first post-operative day, tablet carbimazole was reduced from 40 to 20mg daily for another 5 to 10 days and then stopped. The post-operative follow-up schedule was 1/52, 1/12, 3/12 and 6/12. Following normalization of the thyroid function tests (TSH, T₃ and T₄), the patient was then put on 100µg of levothyroxine daily for life. Control test of thyroid functions were done during each follow-up visit. The TSH, T₃ and T₄ levels returned to normal levels in all cases within two (2) to four (4) weeks post-operatively. At operation, the thyroid gland prepared with the carbimazole was firm, easily mobilised and bleeding was mild, with the use of diathermy (coagulation) machine, hence no need for blood transfusions and their associated risks. There was therefore also less risk of recurrent laryngeal nerve damage and that of the parathyroid glands. Basal metabolic rate dropped significantly from the 3rd to 4th post-operative day.

In this study, pregnant women were excluded to avoid trans-placental effects of carbimazole on the foetus (foetal hypothyroidism) as well as breast-feeding mothers (neonatal effects) [6, 7]. Patients with obstructive airways diseases and cardiac insufficiency were also not included due to the use of esmolol. Adversed drug effects of carbimazole like allergy, bone marrow suppression in the forms of neutropenia and agranulocytosis [6, 7], were not detected. Recurrent thyrotoxicosis, hypothyroidism and other complications anticipated for were not detected in this study.

DISCUSSION

Many of the signs and symptoms of hyperthyroidism in thyrotoxicosis are mediated through the autonomic nervous system, affecting particularly the heart and the nervous system. The beneficial effects of esmolol is that as a selective β₁-adrenoreceptor blocker, it suppresses manifestation of the

disease related to increased sympathetic activity by ameliorating the cardiac and nervous system [1, 2, 3, 4, 5, 24]. Esmolol also works to improve negative nitrogen balance and decreases oxygen consumption, heart rate and cardiac output [3, 4].

Carbimazole acts by inhibiting the iodide oxidation and organization steps of thyroxine synthesis, and it also acts to reduce conversion of (T₄) thyroxine to (T₃) tri-iodothyronine hormones [8, 9]. Carbimazole, 40mg was taken orally daily for 7 to 10 days by thyrotoxic patients prior to sub-total thyroidectomy for Grave's disease, to reduce thyroid hormones synthesis and secretion as well as its peripheral conversion of T₄ to T₃[28, 30] and combined with intraoperative esmolol usage; these results were comparable with the results of [24, 25, 33], who combined β -blocker, iodine and high doses of steroid to rapidly facilitate safe surgery in emergency thyrotoxic patients due to hyperthyroidism.

Esmolol intravenous dosage of 1mg/kg bolus over 30 seconds, followed by a 150-300mg/kg/minute infusion was administered intra-operatively for patients with high pulse rate (≥ 120 bpm). This prevented possible cardiac failure, arrhythmias or cardiac arrest. This concurs with results from [4, 5, 24].

Patients with conditions contraindicated for the use of β_1 -blockers such as brady-arrhythmias, raynaud's syndrome, or patients on monoamine oxidase inhibitors were excluded from this study. Esmolol does not have significant adverse effects on the bronchial tree, nonetheless, patients with obstructive airways diseases, bronchial asthma inclusive, were also excluded from the study. Transient complications usually seen post-operatively were monitored and observed for, including hypoparathyroidism, bleeding or haematoma, wound infection, tracheal collapse, recurrent laryngeal nerve damage but none was detected in all cases. This outcome might have been due to the continuous intravenous infusion of esmolol intra-operatively to control haemodynamics intra-operatively and enhanced by the pre-operative use of carbimazole. [34] reported the use of β -blockers for 5-7days postoperatively to avert the risk of thyroid storm, we did not, but no postoperative thyroid storm incidence was recorded. The use of β -blocker (esmolol), help reduced thyroid vascularity, allowed safe mobilization of the gland and resection during surgery, thereby minimised the risk of damage to neighbouring structures, that was contrarily to studies by Lennigist in 1985[33].

From the first post-operative day (1st POD), carbimazole dosage was reduced from 40 to 20mg daily for 7 to 10 days and then stopped. It was noted that patient's pulse rate returned to normal 3 to 4 days after surgery. Exophthalmos, heat-flashes and other signs and symptoms also reduced gradually to normal over 2 to 4 weeks. In all cases, the anaesthetist gave intravenous atropine intra-operatively to reduce oro-pharyngeal secretions, while using intravenous propofol, suxamethonium and gaseous halothane and oxygen to induce and maintain the anaesthesia by endo-tracheal intubation. The intra-operative administration of esmolol may have prevented the occurrence of thyroid storm.

Surgical thyroid removal (thyroidectomy) partial or total is the oldest therapy for Grave's disease. It is also highly recommended for patients who plan to eventually become pregnant or patients who react to antithyroid drugs (ATDs) to avoid undue medication and radiation side effects. Thyroidectomy also has the advantage of allowing direct tissue examination and for histopathology purposes.

Even though strong iodine solution is usually given 7 to 10 days prior to surgery with or without other agents to decrease vascularity and friability of the thyroid gland, this study did not use any iodine preparation as stated in the literature [24], but the results were similar; unfortunately too, iodine solutions are not available in many countries [24] Ghana inclusive.

CONCLUSION

This study confirms that the combined use of tablet carbimazole pre- and post-operatively, together with intra-operative intravenous esmolol is safe in the management of Grave's disease (thyrotoxicosis) by sub-total thyroidectomy particularly in resource limited settings in developing countries like Ghana.

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