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Review Article

CLINICAL PRACTICE

Risk of perioperative thyroid storm in hyperthyroid patients: a systematic review

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Abstract

Background: Thyroid storm is a feared complication in patients with hyperthyroidism undergoing surgery. We assessed the risk of thyroid storm for different preoperative treatment options for patients with primary hyperthyroidism undergoing surgery.
Methods: Pubmed, EMBASE, and The Cochrane Library were searched systematically for all studies reporting on adult hyperthyroid patients undergoing elective surgery under general anaesthesia. Selected studies were categorised based on preoperative treatment: no treatment, antithyroid medication (thionamides), iodine, β-blocking medication, or a combination thereof. Treatment effect, that is restoring euthyroidism, was extracted from the publications if available. Risk of bias was assessed using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) or the Cochrane Risk of Bias tool for randomised studies.
Results: The search yielded 7009 articles, of which 26 studies published between 1975 and 2020 were selected for critical appraisal. All studies had moderate to critical risk of bias, mainly attributable to risk of confounding, classification of intervention status, and definition of the outcome. All studies reported on thyroidectomy patients. We found no randomised studies comparing the risk of thyroid storm between treated and untreated patients. Cases of thyroid storm were reported in all treatment groups with incidences described ranging from 0% to 14%.
Conclusion: Evidence assessing the risk of perioperative thyroid storm is of insufficient quality. Given the seriousness of this complication and the impossibility of identifying patients at increased risk, preoperative treatment of these patients remains warranted.

Keywords: hyperthyroidism; perioperative; thyroid crisis; thyroid storm; thyrotoxicosis; thyrotoxic crisis

Editor's key points

- Guidelines advise preoperative treatment of hyperthyroid patients with thionamides, iodine, or β-blockers (or a combination of these) until a euthyroid state is achieved, but evidence supporting these guidelines is lacking.
- In this systematic review, the authors present evidence that preoperative treatment does not safeguard a euthyroid or hyperthyroid patient against perioperative thyroid storm.
- However, given the danger of the complication and the difficulty in identifying patients at particular risk, preoperative treatment of these patients is still warranted.

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Hyperthyroidism is a relatively common condition with an estimated prevalence between 1% and 3%, of which approximately 25% to 50% is subclinical.[1–3] A rare but feared complication of hyperthyroidism is a thyroid storm.[4] In this hypermetabolic state, atrial fibrillation, congestive heart failure, and liver failure can develop,[5] and when left untreated, mortality rates between 8% and 25% are reported.[6]

Although the exact pathophysiological mechanism underlying thyroid storm has not been elucidated, sudden fluctuations in physical stress such as trauma and surgery can provoke a thyroid storm. Anaesthesiology[7–13] and most.[14–16] but not all,[17] internal medicine textbooks and the American Association of Endocrine Surgeons Guidelines[6,18] therefore advise to treat these patients before surgery to prevent thyroid storm. Treatment options are antithyroid medication (thionamides) until a euthyroid state is achieved, iodide therapy to decrease the production of thyroid hormones and inhibit hormone secretion, β-blocking medication until haemodynamic stability is achieved, or a combination of these drugs. Of course, forewarned is forearmed, and, as a result, protocols recommending these preventive treatment strategies are widely used in perioperative practice. However, none of these textbooks refer to studies that provide evidence that preoperative treatment of hyperthyroidism decreases the incidence of thyroid storm.

Quantifying the risk of developing thyroid storm, both in treated and untreated hyperthyroid patients, could prove to be valuable in weighing the risk of thyroid storm *vs* the potential benefits of postponing surgery to achieve perioperative euthyroidism. This led to our primary research question: What is the risk of perioperative thyroid storm in surgical hyperthyroid patients with and without one of the aforementioned preoperative antithyroid treatment regimens? To this aim, we conducted a systematic search of the literature including all studies investigating untreated and pretreated hyperthyroid patients undergoing surgery under general anaesthesia and reporting on perioperative and postoperative morbidity associated with thyroid storm, occurrence of thyroid storm, or both.

Methods

Criteria for considering studies for this review

Types of studies

All original research reports that studied the risk of thyroid storm after surgery under general anaesthesia in hyperthyroid patients were considered for inclusion regardless of study design. Non-systematic reviews, conference abstracts, and studies in languages other than English and Dutch were excluded. Owing to the rarity of this outcome, case reports and case series were included. We defined case series as a description of selected cases without a prespecified research question at the point of data collection.

Targeted population

We included studies on adult (≥18 yr) patients undergoing any type of surgery under general anaesthesia. Studies in which preoperative hyperthyroidism was not objectified by laboratory findings but merely diagnosed based on clinical signs were excluded for further data analysis. To obtain an as homogeneous population as possible, only studies reporting on patients with primary hyperthyroidism were included, resulting in studies reporting on secondary and tertiary hyperthyroidism and exogenous causes of thyrotoxicosis (amiodarone induced thyrotoxicosis, molar pregnancy, pituitary tumours etc.) to be excluded from the current review. This was decided because molar pregnancy and pituitary tumours are very rare causes, and the preoperative treatment of amiodarone-induced thyrotoxicosis is different from the preoperative treatment of primary hyperthyroidism. Furthermore, in this particular patient group, it is difficult to distinguish between symptoms associated with the underlying cardiac arrhythmia requiring amiodarone treatment and possible superimposed symptoms because of thyroid storm.

Targeted intervention and comparator

As the course of action concerning preventive preoperative treatment of the hyperthyroid patient has changed over the years, we included studies reporting on hyperthyroid patients undergoing surgery, either or not preventively treated with antithyroid medication, β-blockers, iodine preparations, corticosteroids, or a combination of these medications. To ease interpretation of the results, we divided the studies describing patients who received an intervention into four groups (the comparator being group 1):

1. Hyperthyroid patients not preventively treated before surgery
2. Hyperthyroid patients preventively treated before surgery using solely antithyroid medication
3. Hyperthyroid patients preventively treated before surgery using solely β-blocking medication
4. Hyperthyroid patients preventively treated before surgery using a combination of medications
5. Studies comparing different preventive treatment strategies

Studies in which preoperative treatment regime was not clearly described were excluded. Preoperative treatment >24 h before surgery was considered as relevant preventive or preoperative treatment of the patient.

Targeted outcome

We included all studies reporting on the occurrence of thyroid storm and case reports reporting on detailed associated symptoms of thyroid storm. If occurrence of thyroid storm was not specifically reported, but associated symptoms included in the Burch–Wartofsky score were, the Burch–Wartofsky score was calculated (Table 1).[5] A Burch–Wartofsky score >45 was considered suggestive of thyroid storm. Importantly, not all potential studies included would report the Burch–Wartosfky score themselves, as we expected to find studies dating from before the implementation of this score. When a study did not specifically report on thyroid storm or predefined symptoms thereof, the study was excluded from further analysis. Follow-up duration was determined to be at least 3 days postoperatively. As a secondary outcome, we included information on mortality.

Search strategy

We conducted a systematic search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary file 1). We systematically searched Pubmed, EMBASE, and The Cochrane Library for

Table 1 Burch and Wartofsky scoring system. A score of 45 or greater is highly suggestive of thyroid storm; a score of 25–44 is suggestive of impending storm, and a score below 25 is unlikely to represent thyroid storm. From: Burch and Wartofsky.[5]

Diagnostic parameters	Score
Thermoregulatory dysfunction (temperature, °C)	
37.2–37.7	5
37.8–38.2	10
38.3–38.8	15
38.9–39.2	20
39.3–39.9	25
≥40.0	30
Central nervous system disturbance	
Absent	0
Mild	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizures, coma)	30
Gastrointestinal–hepatic dysfunction	
Absent	0
Moderate (diarrhoea, nausea/vomiting, abdominal pain)	10
Severe	20
Heart rate (beats min^{-1})	
90–109	5
110–119	10
120–129	15
130–139	20
≥140	25
Congestive heart failure	
Absent	0
Mild (pedal oedema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary oedema)	15
Atrial fibrillation	
Absent	0
Present	10
Precipitating event	
Absent	0
Present	10

all relevant literature using different combinations of the keywords 'hyperthyroidism', 'surgery' or 'anaesthesia', and 'thyroid storm' (Supplementary files 2 and 3). In addition, all symptoms of thyroid storm included in the Burch–Wartofsky score were used as synonyms for thyroid storm to find all literature reporting on situations suggestive of thyroid storm.[5] Searches were updated using time filters. The last search update was performed on April 9, 2021.

Data collection and analysis

Selection of studies

After removing duplicates, title and abstract of all articles were verified for relevance. Selected articles were screened full text using pre-defined inclusion and exclusion criteria (Fig. 1). The reference lists of all included studies were checked for additional publications until no further publications were found.

Assessment of risk of bias in included studies

Methodological quality, relevance, and validity of all included cohort studies were assessed using pre-defined criteria. The ROBINS-I tool (Risk of Bias In Non-randomised Studies of Interventions) was used for non-randomised intervention studies.[19] The RoB 2.0 (Risk of Bias tool 2.0) provided by the Cochrane Library was used from randomised studies.[20] The methodological quality was assessed by NM and crosschecked by RVI. Any disagreement was resolved by discussion.

Measures of incidence to be extracted

In cohort studies, absolute risks or relative risks were calculated from available crude data if possible. The case reports were pooled into the groups described above. In the results, the number of patients included in these case reports developing thyroid storm are described in relation to the total number of patients described in case reports within this category.

Results

The search yielded a total of 7691 articles; after removal of duplicates 7009 articles were available for screening. Of these, 175 met our domain, determinant, and (possibly) our outcome on their title/abstract. Potentially relevant articles based on their title (abstract was not available in most cases) that could not be retrieved full text are listed in Supplementary file 4. The main reason for not retrieving these articles is that most of them are published before 1995. After full text screening, a total of 25 cohort studies were obtained meeting our inclusion and exclusion criteria[21–45] and 29 case reports/series were collected,[46–75] One study was excluded because it was a preliminary report of another included study.[76] Cross-reference check of included studies yielded five potential additional relevant articles, of which four were not included in the current search because they did not report on thyroid storm or its signs and symptoms in their abstract. These studies could be retrieved full text, of which one was excluded because there was no report on the occurrence of thyroid storm[77] and the other three (one cohort study, two case series) were added to the search results,[66,78,79] yielding a total of 26 cohort studies and 31 case reports/series. One study was not included in the search because it was unavailable in Pubmed, EMBASE, or Cochrane.[80]

Risk of bias

Methodological data of the included studies can be found in detail in the critical appraisal table (Supplementary file 5). Of the 26 included studies, only one was a prospective randomised trial which scored high risk of bias.[21] The other 25 studies were either prospective or retrospective cohort studies, one being a case-control study comparing hyperthyroid patients with a sample of control patients rendered euthyroid.[79] Four of these 23 studies scored as having moderate risk of bias,[24,28,29,36] 20 studies scored as having a serious risk of bias,[22,23,25–27,30–35,37,38,40–45,79] and one study scored as having a critical risk of bias.[39] Bias was mainly caused by confounding issues, as there was a lack of randomisation, and confounding was not (or only limited) accounted for in all studies. In addition, there were problems with classification of intervention status, as most of the studies were descriptive and classification of intervention status could have been influenced by the risk of the outcome (thyroid storm). Another important issue is definition of the outcome: most studies do not define the occurrence of

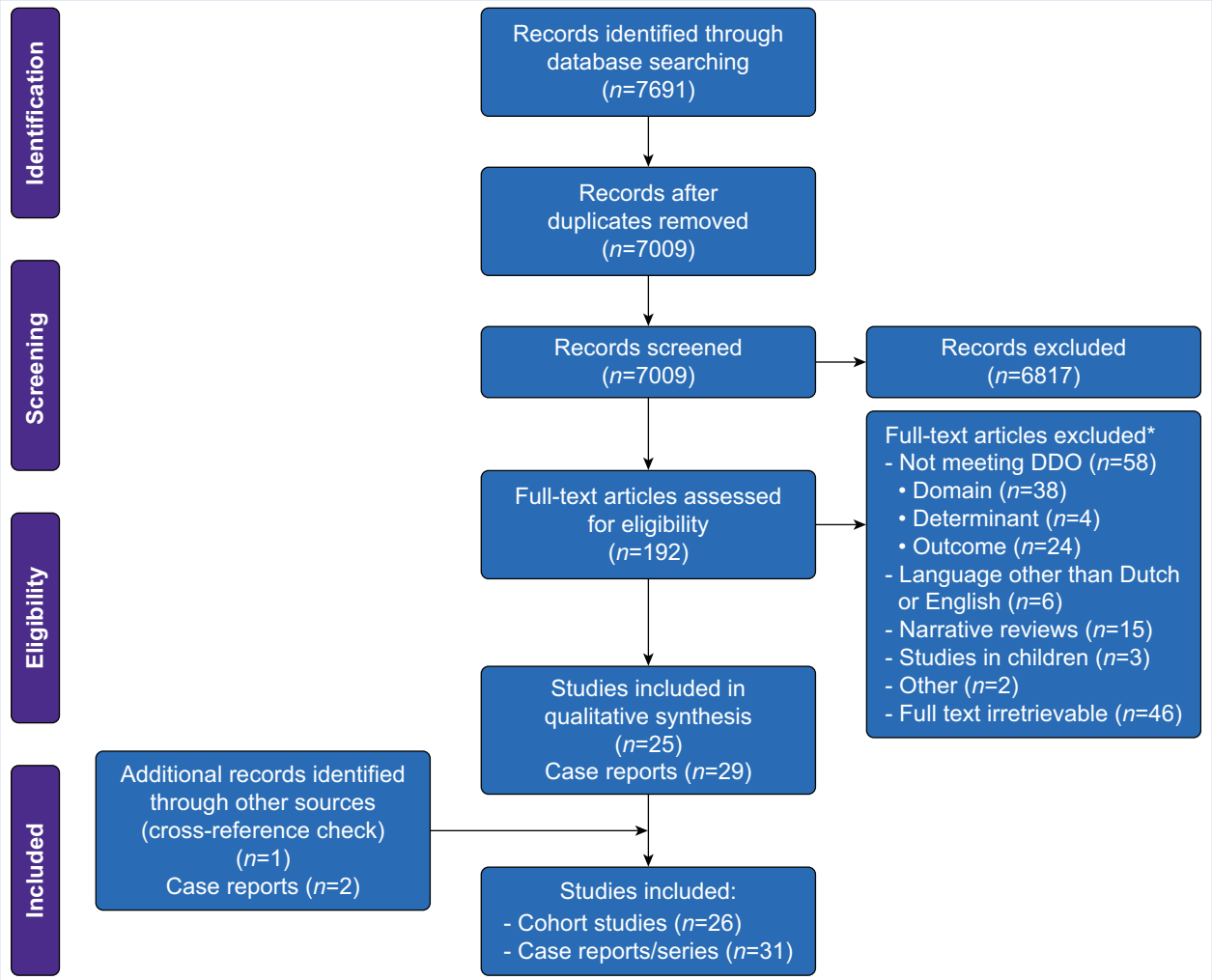

Fig 1. Flowchart of the literature review. *A total of 58 articles did not meet domain, determinant, outcome (DDO) criteria. Domain criteria were not met when articles described emergency surgery (n= 1), locoregional anesthesia (n=7), when storm was already present preoperatively (n=6), or when a diagnosis of primary hyperthyroidism was not met (n=1), or not laboratory confirmed preoperatively or before treatment (n=24). Articles were excluded based on determinant information when the preoperative treatment was not specified (n=4). Articles were excluded based on outcome information when no information on thyroid storm was explicitly provided; one article was excluded because thyroid storm had a late presentation that was not directly related to the surgical procedure (>21 days after surgery). Two studies were excluded for other reasons than provided in the flowchart: one of them was excluded because it focused only on the physiological aspects of thyroid hormone kinetics, the other because it was a conference abstract, which was not clear based on title/abstract screening alone.

thyroid storm, and it is unclear how this outcome was measured or excluded. Although not incorporated in the risk of bias assessment tools, in addition, sample size was often not calculated based on thyroid storm as primary outcome. Finally, missing data were poorly reported and accounted for when applicable.

Description of included studies

All studies except one[43] included patients undergoing thyroidectomy. In this study, two out of 84 patients underwent an elective breast biopsy and emergency cholecystectomy respectively, and the remaining patients underwent thyroidectomy.[43] No studies reporting on the outcome thyroid storm after general surgical procedures could be retrieved. The results of the cohort studies are reported in Table 2. Incidences of thyroid storm ranging from 0% to 14% were reported. Details on included cohort studies and case reports are described in Supplementary files 6 and 7, respectively.

Group 1: patients with preoperative hyperthyroidism – not prepared for surgery

None of the included cohort studies described the incidence of thyroid storm in laboratory confirmed hyperthyroid patients that were not preventively treated before surgery. We retrieved eight case reports describing eight hyperthyroid

Table 2 Overall results. Overview of the incidence of thyroid storm in the included studies. Of each study, author, year of publication, number of included patients, preoperative treatment and occurrence of thyroid storm and mortality is described. In case number of patients that received a certain treatment was not reported, *n*=? is noted in this table. *These numbers are reconstructed from the text but are not given explicitly in the original text and therefore there might be errors in estimating them. †Diagnosis thyroid storm was not given in the text, but increased severity of thyrotoxicosis was described, with symptoms of sweating, mental confusion, agitation, tachycardia, and fever. As no values were given, the Burch–Wartofsky score could not be estimated.

Hyperthyroid patients not preventively treated before surgery

Author, year	Patients, *n*	Preoperative treatment	Occurrence of thyroid storm, *n* (%)	Mortality, *n* (%)
No studies were found describing hyperthyroid patients who were not treated before surgery				

Hyperthyroid patients treated before surgery using solely thionamides

Author, year	Patients, *n*	Preoperative treatment	Occurrence of thyroid storm	Mortality
Heimann and Martinson,[30] 1975	272	Thionamides, either or not in combination with iodine (*n*=248), toxic adenomas did not receive preoperative treatment (*n*=24)*	1 (0.4%) in the pretreated group (although treatment discontinued early owing to side-effects)	0%

Hyperthyroid patients treated before surgery using solely β-blocking medication

Author, year	Patients, *n*	Preoperative treatment	Occurrence of thyroid storm	Mortality
Caswell and colleagues,[25] 1978	30	β-Blocker (*n*=24) β-Blocker + Lugol's (*n*=6)	0%	0%
Lee and Coffey,[31] 1982	160	β-Blocker	0%	0%
Toft and colleagues,[38] 1978	100	β-Blocker	0%	0%

Hyperthyroid patients treated before surgery using a combination of medications

Author, year	Patients, *n*	Preoperative treatment	Occurrence of thyroid storm	Mortality
Al Jassim and colleagues,[23] 2018	67	Different combinations using thionamides (*n*=57), potassium iodine (*n*=18), steroids (*n*=5), β-blockers (*n*=23). Seven cases were not treated with medication	0%	0%
Cipolla and colleagues,[26] 2019	594	Thionamides, combined with either a β-blocker (*n*=432) or Lugol's (*n*=152)	0%	0%
Fischli and colleagues,[28] 2016	10	A combination of Lugol, steroid and a β-blocker	0%	0%
Panzer and colleagues,[35] 2004	17	A combination of thionamides, iopanoic acid and steroid (*n*=15) Thionamides only (*n*=2)	0%	0%
Peden and colleagues,[36] 1982	17	A combination of β-blocker and potassium iodide	0%	0%
Rodigas and colleagues,[44] 1977	22	A combination of thionamides and Lugol's (*n*=11) A combination of β-blockers and Lugol's (*n*=4) A combination of thionamides, β-blockers and Lugol's (*n*=7)	1 in the third group (14%)	0%
Shinall and collegaues,[37] 2013	165	Different combinations using thionamides (*n*=156), potassium iodide (*n*=3), steroids (*n*=15) and β-blockers (*n*=92)	0%	0%
Tomaski and colleagues,[39] 1997	14	Different combinations using thionamides (*n*=10), β-blockers (*n*=?) and sodium ipodate	0%	0%
Vital and colleagues,[40] 2017	99	Different combinations using thionamides (*n*=80), β-blockers (*n*=79) and potassium iodide (*n*=?)	0%	0%
Yamanouchi and colleagues,[41] 2020	186	Potassium iodide, either or not in combination with corticosteroid, β-blocker, or both	0%	0%

Continued

Table 2 Continued

Studies comparing different treatment strategies Author, year	Patients, *n*	Preoperative treatment	Occurrence of thyroid storm	Mortality
Adlerberth and colleagues,[21] 1987	30	β-Blockers (*n*=15) Thionamides (*n*=15)	0%	0%
Akram and colleagues,[22] 2020	288	Thionamides + β-blocker (*n*=144) Thionamides (*n*=98) β-Blocker (*n*=14) No treatment (*n*=32)	0%	0%
Ali and colleagues,[24] 2019	266	Regular treatment (thionamide + Lugol's) (*n*=247) Rapid treatment using different combinations of thionamides, β-blockers, steroids, cholestyramine and verapamil (*n*=19)	0%	0%
Feely and colleagues,[27] 1981	64	β-Blocker (*n*=44) Thionamide (*n*=20)	0%†	0%
Haddad and Tibblin,[29] 1988	41	Thionamides (*n*=20) β-Blockers (*n*=21)	0%	0%
Hsieh and colleagues,[45] 2020	248	All: different combinations of β-blockers, Lugol's, steroids, cholestyramine (*n*=248) + Antithyroid drugs (*n*=231) No antithyroid drugs (*n*=17)	0%	0%
Lee and colleagues,[32] 1986	108	β-Blockers (*n*=22) Thionamides + β-blockers (*n*=86)	1 in the β-blocker group (4.5%)	1 (4.5%)
Lukomsky and colleagues,[33] 1984	1261	Three groups 1. Plummer's method (iodine), either or not in combination with corticosteroids (adrenal insufficiency) (*n*=94) 2. Bay's method (iodine), either or not in combination with corticosteroids (*n*=872) 3. Thionamides (*n*=295)	Group 1: 2 (2.1%) Group 2: 2 patients (0.2%) Group 3: 0 (0%)	2 (2.1%) 2 (0.2%) 0 (0%)
Melliere and colleagues,[34] 1988	500	Three groups: 1. Lugol + 'tranquilizer' + hydrocortisone (*n*=100) 2. Thionamides + 'tranquilizer' + β-blocker on indication (*n*=125) 3. Thionamides + β-blocker (*n*=275)	Group 1 + 2: 9 (4%) Group 3: 0 (0%)	Unknown Unknown
Nair and colleagues,[79] 2018	168	Thionamides, either or not in combination with β-blocker (*n*=168) Lithium + β-blocker + corticosteroid (*n*=6)	0%	0%
Yu and colleagues,[42] 2018	29	1. Thionamides (*n*=12) 2. Different combinations of thionamides (*n*=13), β-blockers (*n*=8) and Lugol (*n*=5)	0%	0%
Zonszein and colleagues,[43] 1979	84	β-Blocker (*n*=72) Thionamide + β-blocker (*n*=12)	0%	0%

patients undergoing surgery under general anaesthesia without preventive preoperative treatment.[46–51,53] Five of these patients developed thyroid storm.

Group 2: patients prepared solely with antithyroid medication

One study reported on patients prepared for surgery with solely antithyroid medication.[30] Of the 272 included patients, a total of 17 patients were switched to iodine because of the side-effects of the antithyroid medication. One of these 17 patients developed thyroid storm. The definite status of this patient (euthyroid or hyperthyroid) at the time of surgery is not described. We retrieved six case reports describing six patients who were preventively treated before surgery using solely thionamides.[54,64,67,69,72,74] Five of them developed (a full or impending) thyroid storm in the perioperative course.

Group 3: patients prepared solely with β-blockers

In three studies, two retrospective cohorts of 30 and 100 patients and one prospective cohort 160 patients, hyperthyroid patients were prepared with solely β-blocking medication before surgery.[25,31,38] These patients were biochemically hyperthyroid at the time of surgery. In none of these studies a thyroid storm occurred. We retrieved five case reports/series

that described a total of 23 patients undergoing surgery using solely β-blockers as preventive treatment in which one case of thyroid storm occurred.[56–60]

Group 4: patients prepared with a combination of medications

In 10 studies, patients received a combination of different medications.[23,26,28,35–37,39–41] Sample sizes varied from 10 to 594 patients. Medication regimes in these studies are shown in Table 2 and in more detail in Supplementary file 5. In only one of these studies (n=22), thyroid storm occurred. This occurred in the immediate postoperative period in two patients (14%) being treated with a combination of propranolol, propylthiouracil, and Lugol's iodine.[44] Baseline characteristics and underlying thyroid disease or severity of hyperthyroidism were not described. In the other studies, no thyroid storm occurred. In one study, vital signs were compared between level of preoperative thyroid level control, classified as good (FT3 $\leq$6.0 pg ml^{-1}, n=126), fair (6.0 < FT3 $\leq$ 10.0 pg ml^{-1}, n=35), or poor (FT3 >10.0 pg ml^{-1}, n=25).[41] Heart rate 1 h after beginning general anaesthesia was higher in the poor control group than in the good control group (P<0.05), and the proportion of patients given β-blockers intraoperatively was higher in the poor control group compared with the other groups (P<0.01 each). Twelve case reports reporting on 23 patients receiving a combination of medications as preventive treatment strategies report a total of three patients developing thyroid storm, each of them being treated with a different treatment regimen.[55,61–63,65,66,68,70,71,73,75,78]

Group 5: studies comparing different treatment strategies

A total of 12 studies were found to compare different treatment strategies preoperatively.[21,22,24,27,29,32–34,42,43,45,79] One study compared patients with controlled Graves' disease (n=12) with patients with uncontrolled Graves' disease (n=17), in which uncontrolled Graves' disease was defined as persistent hyperthyroidism with an FT4 > 1.7 ng dl^{-1} and TSH < 0.3 μIU ml^{-1}.[42] In both groups most patients received antithyroid drugs and some patients received iodine (Lugol). In the group of patients with uncontrolled Graves' disease, some patients also received β-blockers. In both groups no thyroid storm occurred, and neither were there any significant differences in perioperative vital signs between both groups. Another study compared 168 overtly hyperthyroid patients being treated with thionamides, either or not in combination with β-blockers (n=71) to a small group of clinically euthyroid patients being treated with a combination of lithium carbonate, propranolol and dexamethasone (n=6).[79] Thyroid storm did not occur in both patient groups. In a more recent retrospective study, 248 patients with hyperthyroidism who were initially treated with antithyroid drugs (thionamides) and underwent thyroidectomy were described.[45] Of these 248 patients, 17 were discontinued from their antithyroid drugs owing to side-effects and only treated with different combinations of β-blockers, Lugol's iodine, steroids, and cholestyramine. There were no significant differences between patient characteristics (age, sex, comorbidities, cause of hyperthyroidism). The only significant difference between groups was a higher use of β-blockers in the non-antithyroid drug group. Thyroid storm did not occur in either patient group.

Comparing treatment strategies to iodine alone

Two retrospective studies from 1988 and 1984 reported on comparing treatment strategies in which iodine alone was compared with other regimes. In one of them, the outcome of surgery in 500 patients successfully 'rendered euthyroid' with different combinations of medications was described.[34] One group was prepared for surgery with iodine and a not further specified 'tranquilizer' (group 1), one group with carbimazole and a not further specified 'tranquilizer' (group 2), in which some patients also received propranolol, and the last group receiving carbimazole and propranolol (group 3). All patients were euthyroid, except for 16 patients in group 1 who were still hyperthyroid at the time of surgery. In this study, nine patients developed a thyroid storm in groups 1 and 2 (number of patients in each group not specified). The other study compared methimazole (group 3, n=295) with several forms of iodide therapy, namely the Plummer's method in combination with corticosteroid therapy for those with adrenal insufficiency (group 1, n=94) and the Bay's method – large doses of iodine combined with corticosteroid therapy for those with adrenal insufficiency (group 2, n=872).[33] Thyroid status was only tested in 25 patients preoperatively, of whom 22 patients were reported to achieve euthyroidism after treatment with antithyroid medication. A total of four patients, two in group 1 and two in group 2 (both iodine therapy groups) developed thyroid storm and died, suggesting an absolute risk for thyroid storm of 0.23% using the Plummer method and an adjusted absolute risk of 2.1% using the higher dosage of iodine according to the method of Bay.

Comparing β-blocking drugs to antithyroid drugs or a combination of the two

Three studies, with sample size 30–64 patients, compared β-blocking drugs with antithyroid drugs, consequently also comparing biochemical hyperthyroid and euthyroid state preoperatively.[21,27,29] None of these three studies reported occurrence of thyroid storm in either group. Two studies compared β-blocking drugs alone with a combination of β-blocking medication and antithyroid medication.[32,43] In one of these studies, 22 patients received propranolol alone and 86 patients received a combination of propranolol and propylthiouracil.[32] It was not described whether patients were euthyroid or hyperthyroid at the moment of surgery. One of the patients in the propranolol group developed high fever (exact temperature not specified), tachycardia <110 min^{-1}, sweating, and comatose state in the postoperative period. The authors did not calculate the Burch–Wartofsky score but based on the clinical findings it was 60–75 points, depending on exact temperature of the patient. This is highly suggestive of thyroid storm. In the other study, 72 patients were treated with propranolol alone and 12 patients were treated with a combination of thionamide and propranolol (not achieving euthyroid state preoperatively).[43] No cases of thyroid storm occurred in either group.

Comparing different guidelines

One study reported on 288 patients undergoing thyroidectomy, being treated with either methimazole combined with a β-blocker (50% of patients), methimazole only (34% of patients), β-blocker only (5% of patients), or no treatment.[22] Of these patients, 72% were euthyroid at the moment of surgery,

whereas 28% were hyperthyroid. No patients in this cohort developed thyroid storm. They also performed a sub-analysis of 197 patients who were divided into either prepped conform American Thyroid Association guidelines (ATA-prepped, 52% of patients) or non-ATA prepped. Except for fewer episodes of intraoperative tachycardia (0.3 *vs* 4.5, $P=0.04$), no differences in peak systolic blood pressure, number of episodes with a systolic blood pressure of >180 mm Hg, mean operating time, length of stay, and overall complications were found.

Another study compared outcomes in 266 patients being prepared for surgery regularly with an antithyroid drug, thyroxine and Lugol's iodine, with patients being prepared using a rapid preparation protocol ($n=19$).[24] No patient developed thyroid storm.

Discussion

Our aim was to quantify the risk of thyroid storm in hyperthyroid patients undergoing surgery and compare this risk between different treatment strategies. Although no studies were found with sufficient subjects included to reliably estimate the risk of thyroid storm, we have found studies reporting risks ranging from 0% to 14%. No studies compared unprepared hyperthyroid patients to patients in a (clinically) euthyroid state after treatment with thionamides, iodine solution, β-blockers, and/or corticosteroids before surgery. Therefore, given the seriousness of the complication, preoperative treatment of patients undergoing elective surgery is still warranted.

We found one study that reported on the association of a variety of postoperative complications such as cardiovascular events, cardiac failure, infections, stroke, and neurological complications to preoperative thyroid status (either euthyroid or hyperthyroid) in a cohort of older orthopaedic patients.[81] The incidence of these various complications was higher in hyperthyroid patients, but the distribution of these complications did not differ significantly between euthyroid and hyperthyroid patients. Thyroid storm was not measured in this study.

The current paradigm, as advised in anaesthesiology, internal medicine, and surgical textbooks, is to preventively treat all hyperthyroid patients for surgery using a diversity of medication, preferably a combination of strategies: reducing thyroid hormone synthesis and secretion by thionamides, iodine solutions, or both, protecting the vascular system and yielding haemodynamic stability by β-blockers, and reducing circulating free T3 levels and replacing cortisol in adrenal insufficient patients by corticosteroids. Our aim was to compare the risk of thyroid storm between different preoperative treatment strategies. In the studies included in this literature review, thyroid storm occurred regardless of preoperative treatment received, and more interestingly, both in euthyroid and hyperthyroid patients.

This is the first review of the literature to present an overview of the currently available evidence concerning the risk of perioperative thyroid storm in hyperthyroid patients. Although we are convinced this review covers all relevant literature, several limitations in the study design and included studies must be acknowledged.

First, because we aimed to retrieve all literature describing the risk of thyroid storm in hyperthyroid patients undergoing surgery, we did not apply time limitations to our search. As a result, we had trouble retrieving the older articles' full text. We have included this list of unretrieved articles in Supplementary file 3.

Second, we only included studies written in the English and Dutch language, which could potentially lead to language bias. However, because we were looking for the evidence supporting our international guidelines, we expected this evidence to be written in English.

Third, formulation of the risk of thyroid storm and comparing risks between untreated patients and preventively treated patients are based on a large variety of studies, which show large heterogeneity and methodological shortcomings. All studies had moderate to critical risk of bias. Thyroid storm was not the primary outcome in all but one of the included studies, and therefore no standardised criteria for diagnosing thyroid storm were used. And as the incidence of thyroid storm is probably very low, all studies likely lack statistical power to provide reliable estimates of the incidence of thyroid storm, let alone a difference in occurrence between treatment strategies. Estimated incidences provided in this manuscript based on the included studies should therefore be taken with caution. The definition of hyperthyroidism differed among studies and most of the older studies used insufficient criteria for diagnosing hyperthyroidism or euthyroidism. Sensitive assays for measuring TSH were not available at that time, and diagnosis of hyperthyroidism was mainly made on the ground of clinical signs and concentration of total T3, T4, or both. Moreover, the plasma kinetics of total T3/T4 (TT3/TT4) and free T3/T4 (fT3/fT4) are substantially different with a much longer half-life of fT3/fT4 compared with TT3/TT4.[82] As a result, a patient with a normalised TT3/TT4 could still have elevated fT3/fT4 concentrations, and potentially consequently a higher risk of thyroid storm.[82] Furthermore, because most studies were not randomised, selection bias might have occurred, as the more therapy-resistant individuals might have been placed in more aggressive treatment groups. Occurrence of thyroid storm in those treatment groups might therefore also be related to underlying patient characteristics, which were seldomly accounted for in the included studies. In addition, general patient and hospital characteristics differed among studies, for example on age, ethnicity, and care setting. Based on these arguments, and the lack of comparative studies, conducting a meta-analysis on this subject was not possible. Furthermore, although thyroid storm was described in all patient groups, publication bias of case reports cannot be ruled out. Because of the lack of a denominator, the case report data were not used to estimate thyroid storm incidence. What we can derive from these case reports is that thyroid storm is a serious complication that can occur in every patient group, despite pretreatment of the patient.

In conclusion, this review shows the lack of evidence concerning the risk of perioperative storm in prepared and unprepared hyperthyroid patients. There are no studies comparing the risk of thyroid storm between untreated hyperthyroid patients and patients preventively treated to achieve (clinical) euthyroidism. A thyroid storm can appear despite of the choice of preoperative treatment strategy. Therefore, preoperative treatment does not safeguard a euthyroid or hyperthyroid patient from a thyroid storm. Because of the rarity of thyroid storms, it is virtually impossible to perform an adequately powered randomised study comparing treatment strategies. A reliable case-control study is also not achievable as thyroid storm is not routinely registered in hospital records.

Although this review underlines the lack of absolute evidence on the risk of thyroid storm, current guidelines on preoperative treatment in elective surgical patients should be

followed, given the seriousness of this complication and the impossibility of identifying patients at increased risk.

Authors' contributions

Study concept: RVI
Review question and study design: NM, RVI
Title/abstract screening, full text screening, and data extraction from the articles: NM, JD
Critical appraisal reporting: NM
Critical appraisal cross-checking: RVI
Drafted the manuscript: NM, RVI
Revised the content of the manuscript: WJMS, EJMND, SF, CJK
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.06.043.

References

1. Bjoro T, Holmen J, Kruger O, et al. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT). *Eur J Endocrinol* 2000; **143**: 639–47
2. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000; **160**: 526–34
3. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): national health and nutrition examination survey (NHANES III). *J Clin Endocrinol Metab* 2002; **87**: 489–99
4. Noble KA. Thyroid storm. *J Perianesth Nurs* 2006; **21**: 119–22. quiz 23–5
5. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin N Am* 1993; **22**: 263–77
6. Patel KN, Yip L, Lubitz CC, et al. The American association of endocrine surgeons guidelines for the definitive surgical management of thyroid disease in adults. *Ann Surg* 2020; **271**: E21–93
7. Jeffrey J, Schwartz SA, Rosenbaum ASH. Endocrine function. In: Barash PG, Cahalan MK, Cullen BF, et al., editors. *Clinical anesthesia*. 8th edn. Philadelphia: Wolters Kluwer Lippincott, Williams & Wilkins; 2017. p. 2431–5
8. Wijeysundera DN, Schweitzer BJ. Pre-operative evaluation. In: Miller RD, editor. *Miller's anaesthesia*. 8th edn. Philadelphia: Elsevier Saunders; 2015. p. 1115–6
9. Butterworth Iv JF, Mackey DC, Wasnick JD. Anesthesia for patients with endocrine disease. In: *Morgan & Mikhail's clinical anesthesiology*. 6th edn. New York: McGraw-Hill Education; 2018
10. Kiefer J, Mythen M, Roizen MF, Fleisher LA. Anesthetic implications of concurrent diseases. In: Gropper MA, editor. *Miller's anaesthesia*. Philadelphia: Elsevier, Inc.; 2020. p. 999–1064
11. Doyle D, Mannings A. Intercurrent disease and anaesthesia. In: Thompson J, Moppet I, Wiles M, editors. *Smith and Aitkenhead's textbook of anaesthesia*. Elsevier Limited; 2019. p. 400–33
12. Longnecker DE. Evaluation of the patient with endocrine disease and diabetes mellitus. In: Longnecker DE, Brown DL, Newman MF, Zapol WM, editors. *Anesthesiology*. New York: McGraw-Hill Companies, Inc.; 2008. p. 175–6
13. Periris P. Anesthesia for thyroid surgery. In: Murray MJ, Harrison BA, Mueller JT, et al., editors. *Faust's anesthesiology review*. 4th edn. Philadelphia: Elsevier Saunders; 2015. p. 419
14. Wartofsky L. Diseases of the thyroid. In: Fauci AS, Braunwald E, Isselbacher KJ, et al., editors. *Harrison's principles of internal medicine*. 14th edn. USA: R.R. Donnelley and Sons, Inc.; 1998. p. 2012–35
15. Idrose AH. Thyroid disorders: hyperthyroidism and thyroid storm. In: Tintinalli JE, Stapczynski J, Ma O, et al., editors. *Tintinalli's emergency medicine*. 7th ed. China: McGraw-Hill; 2011. p. 1447–53
16. Surgery of the thyroid. In: Jameson JL, De Groot LJ, De Kretser DM, et al., editors. *Endocrinology adult and pediatric*. Philadelphia: Elsevier-Saunders; 2015. p. 1674–5
17. Salvatore D, Davies TF, Schlumberger MJ, Hay ID, Larsen PR. Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Melmed S, Polonsky KS, Reed Larsen P, Kronenberg HM, editors. *Williams textbook of endocrinology*. 12th edn. Philadelphia: Elsevier-Saunders; 2011. p. 327–475
18. Patel KN, Yip L, Lubitz CC, et al. Executive summary of the American Association of Endocrine Surgeons guidelines for the definitive surgical management of thyroid disease in adults. *Ann Surg* 2020; **271**: 399–410
19. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Br Med J* 2016; **355**: i4919
20. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Br Med J* 2019; **366**: l4898
21. Adlerberth A, Stenstrom G, Hasselgren PO. The selective beta 1-blocking agent metoprolol compared with antithyroid drug and thyroxine as pre-operative treatment of patients with hyperthyroidism. Results from a prospective, randomized study. *Ann Surg* 1987; **205**: 182–8
22. Akram S, Elfenbein DM, Chen H, Schneider DF, Sippel RS. Assessing American Thyroid Association guidelines for total thyroidectomy in Graves' disease. *J Surg Res* 2020; **245**: 64–71
23. Al Jassim A, Wallace T, Bouhabel S, et al. A retrospective cohort study: do patients with graves' disease need to be euthyroid prior to surgery? *J Otolaryngol Head Neck Surg* 2018; **47**: 37
24. Ali A, Debono M, Balasubramanian SP. Outcomes after urgent thyroidectomy following rapid control of thyrotoxicosis in Graves' disease are similar to those after elective surgery in well-controlled disease. *World J Surg* 2019; **43**: 3051–8

25. Caswell HT, Marks AD, Channick BJ. Propranolol for the pre-operative preparation of patients with thyrotoxicosis. *Surg Gynecol Obstet* 1978; **146**: 908–10
26. Cipolla C, Graceffa G, Calamia S, et al. The value of total thyroidectomy as the definitive treatment for Graves' disease: a single centre experience of 594 cases. *J Clin Transl Endocrinol* 2019; **16**: 100183
27. Feely J, Crooks J, Forrest AL. Propranolol in the surgical treatment of hyperthyroidism, including severely thyrotoxic patients. *Br J Surg* 1981; **68**: 865–9
28. Fischli S, Lucchini B, Müller W, Slahor L, Henzen C. Rapid pre-operative blockage of thyroid hormone production/secretion in patients with Graves' disease. *Swiss Med Wkly* 2016; **146**: w14243
29. Haddad JF, Tibblin S. Pre-operative treatment of thyrotoxicosis in developing countries: a comparative study of carbimazole and propranolol. *Ann R Coll Surg Engl* 1988; **70**: 357–60
30. Heimann P, Martinson J. Surgical treatment of thyrotoxicosis: results of 272 operations with special reference to pre-operative treatment with anti-thyroid drugs and L-thyroxine. *Br J Surg* 1975; **62**: 683–8
31. Lee TC, Coffey RJ, Currier BM. Propranolol and thyroidectomy in the treatment of thyrotoxicosis. *Ann Surg* 1982; **195**: 766–73
32. Lee KS, Kim K, Hur KB, Kim CK. The role of propranolol in the pre-operative preparation of patients with Graves' disease. *Surg Gynecol Obstet* 1986; **162**: 365–9
33. Lukomsky GI, Ivanova NA, Kabanova GM. Pre-operative treatment of patients with thyrotoxicosis. *Am J Surg* 1984; **147**: 263–5
34. Melliere D, Etienne G, Becquemin JP. Operation for hyperthyroidism. Methods and rationale. *Am J Surg* 1988; **155**: 395–9
35. Panzer C, Beazley R, Braverman L. Rapid pre-operative preparation for severe hyperthyroid Graves' disease. *J Clin Endocrinol Metabol* 2004; **89**: 2142–4
36. Peden NR, Gunn A, Browning MC, et al. Nadolol and potassium iodide in combination in the surgical treatment of thyrotoxicosis. *Br J Surg* 1982; **69**: 638–40
37. Shinall Jr MC, Broome JT, Nookala R, et al. Total thyroidectomy for Graves' disease: compliance with American Thyroid Association guidelines may not always be necessary. *Surgery* 2013; **154**: 1009–15
38. Toft AD, Irvine WJ, Sinclair I. Thyroid function after surgical treatment of thyrotoxicosis. A report of 100 cases treated with propranolol before operation. *N Engl J Med* 1978; **298**: 643–7
39. Tomaski SM, Mahoney EM, Burgess LP, Raines KB, Bornemann M. Sodium ipodate (oragrafin) in the pre-operative preparation of Graves' hyperthyroidism. *Laryngoscope* 1997; **107**: 1066–70
40. Vital D, Morand GB, Meerwein C, et al. Early timing of thyroidectomy for hyperthyroidism in Graves' disease improves biochemical recovery. *World J Surg* 2017; **41**: 2545–50
41. Yamanouchi K, Kuba S, Sakimura C, et al. The pre-operative thyroid function and peri-operative course in patients with graves' disease. *Acta Med Nagasaki* 2020; **63**: 79–86
42. Yu HW, Bae IE, Kim SJ, et al. Comparison of intra-operative vital sign changes during total thyroidectomy in patients with controlled and uncontrolled Graves' disease. *J Clin Med* 2018; **7**: 566
43. Zonszein J, Santangelo RP, Mackin JF. Propranolol therapy in thyrotoxicosis. A review of 84 patients undergoing surgery. *Am J Med* 1979; **66**: 411–6
44. Rodigas P, Sufian S, Kaibara N, Matsumoto T. Surgery of the thyroid gland. *Int Surg* 1977; **62**: 588–91
45. Hsieh LB, Yen TWF, Dream S, Patel D, Evans DB, Wang TS. Peri-operative management and outcomes of hyperthyroid patients unable to tolerate antithyroid drugs. *World J Surg* 2020; **44**: 3770–7
46. Hirvonen EA, Niskanen LK, Niskanen MM. Thyroid storm prior to induction of anaesthesia. *Anaesthesia* 2004; **59**: 1020–2
47. Isley WL, Dahl S, Gibbs H. Use of esmolol in managing a thyrotoxic patient needing emergency surgery. *Am J Med* 1990; **89**: 122–3
48. Kiyama S, Yoshikawa T. Refractory atrial fibrillation in an emergency surgical patient: a sign of untreated thyrotoxicosis. *J Anesth* 1995; **9**: 200–2
49. Lynch BA, Dolan JP, Mann M. Thyrotoxicosis after gastric bypass surgery prompting operative re-exploration. *Obes Surg* 2005; **15**: 883–5
50. Martinelli AM, Fontana JL. Thyroid storm. Potential peri-operative crisis. *AORN J* 1990; **52**: 305–13
51. Park JT, Lim HK, Park JH, Lee KH. Thyroid storm during induction of anesthesia. *Kor J Anesthesiol* 2012; **63**: 477–8
52. Pride W, Smith A, Joseph R. Thyroid storm following rapid sequence intubation. *Am J Emerg Med* 2018; **36**: 2338. e5–6
53. Pugh S, Lalwani K, Awal A. Thyroid storm as a cause of loss of consciousness following anaesthesia for emergency caesarean section. *Anaesthesia* 1994; **49**: 35–7
54. Liang M, Wang H, Tan L, Feng M, Shen Y, Wang Q. Successful treatment of thyrotoxic crisis after esophagectomy in an elderly woman with hyperthyroidism. *Ann Thorac Surg* 2012; **93**: e141–2
55. Pagsisihan DA, Andag-Silva A, Piores-Roderos O, Escobin MA. Rapid pre-operative preparation for thyroidectomy of a severely hyperthyroid patient with graves' disease who developed agranulocytosis. *J ASEAN Fed Endocr Soc* 2015; **30**: 48–52
56. Gerst PH, Fildes J, Baylor P, Zonszein J. Long-acting beta-adrenergic antagonists as preparation for surgery in thyrotoxicosis. *Arch Surg* 1986; **121**: 838–40
57. Hewitt PM, Willcox PA. Thyrotoxic crisis after emergency laparotomy. A case report. *S Afr Med J* 1990; **77**: 645–6
58. Ljunggren JG, Persson B. Pre-operative treatment of thyrotoxicosis with a beta-adrenergic blocking agent. *Acta Chirurg Scand* 1975; **141**: 715–8
59. Starling JR, Thomas Jr CG. Radical mastectomy in a patient with coexistent Graves' disease. *Am J Surg* 1976; **132**: 110–1
60. Vijayakumar HR, Thomas WO, Ferrara JJ. Peri-operative management of severe thyrotoxicosis with esmolol. *Anaesthesia* 1989; **44**: 406–8
61. Bolaji BO, Oyedepo OO, Rahman GA. Anaesthesia management for thyroidectomy in a non-euthyroid patient following cardiac failure. *Niger J Clin Pract* 2011; **14**: 482–5
62. Dial P, Hastings PR. The use of a selective beta-adrenergic receptor blocker for the pre-operative preparation of thyrotoxic patients. *Ann Surg* 1982; **196**: 633–5
63. Grimes CM, Muniz H, Montgomery WH, Goh YS. Intra-operative thyroid storm: a case report. *AANA J* 2004; **72**: 53–5
64. Kandil E, Khalek MA, Thethi T, Abd Elmageed Z, Khan A, Jaffe BM. Thyroid storm in a patient with fulminant hepatic failure. *Laryngoscope* 2011; **121**: 164–6

65. Reber A, Valenti L, Muller S. A patient with Graves' disease scheduled for thyroidectomy with high risk for thyroid storm caused by severe medication nonadherence: anaesthetic and surgical considerations. *Case Rep Anesthesiol* 2019; **2019**: 4781902
66. Thorne AC, Bedford RF. Esmolol for peri-operative management of thyrotoxic goiter. *Anesthesiology* 1989; **71**: 291–4
67. Akin F, Yaylali GF, Bastemir M. The use of lithium carbonate in the preparation for definitive therapy in hyperthyroid patients. *Med Princ Pract* 2008; **17**: 167–70
68. De Ruijter SHW, Muller AF, Van Dalen T. The surgical treatment of Graves' disease. *Ned Tijdschr Geneeskd* 2006; **150**: 1321–5
69. Santhosh MC, Torgal SV, Bhat Pai R, Roopa S, Hegde HV, Rao RP. Intra-operative thyroid storm in a patient with euthyroid multinodular goiter. *Acta Anaesthesiol Taiwan* 2012; **50**: 191
70. Strube PJ. Thyroid storm during beta blockade. *Anaesthesia* 1984; **39**: 343–6
71. Reed J, Bradley 3rd EL. Post-operative thyroid storm after lithium preparation. *Surgery* 1985; **98**: 983–6
72. Dassanayake VEG, Welikala ND, Ramasinghe SL. Delayed recovery from general anaesthesia following thyroidectomy: a "near miss". *Sri Lankan J Anaesthesiol* 2020; **28**: 159–61
73. Perera HI, Selvapalan D, Abayadeera A. Urgent surgery in a poorly controlled hyperthyroid patient. *Sri Lankan J Anaesthesiol* 2020; **28**: 156–8
74. McGonigle AM, Tobian AA, Zink J, King KE. Perfect storm: therapeutic plasma exchange in a thyroid storm patient. *J Clin Apher* 2015; **30**: 95
75. Lee JH. Thyroid storm after coronary artery bypass surgery: a case report. *J Cardiothorac Surg* 2020; **15**: 22
76. Lee TC, Coffey RJ, Mackin J, Cobb M, Routon J, Canary JJ. The use of propranolol in the surgical treatment of thyrotoxic patients. *Ann Surg* 1973; **177**: 643–7
77. Berghout A, Wiersinga WM, Brummelkamp WH. Sodium ipodate in the preparation of Graves' hyperthyroid patients for thyroidectomy. *Horm Res* 1989; **31**: 256–60
78. Tsunoda T, Mochinaga N, Eto T, Yamaguchi M, Tsuchiya R, Izumi M. Lithium carbonate in the preoperative preparation of Graves' disease. *Jpn J Surg* 1991; **21**: 292–6
79. Nair GC, MJ CB, Menon R, Jacob P. Pre-operative preparation of hyperthyroidism for thyroidectomy — role of supersaturated iodine and lithium carbonate. *Indian J Endocrinol Metab* 2018; **22**: 392–6
80. Bergfeldt GL, Ljunggren JG, Hedberg K. Pre-operative treatment of thyrotoxicosis with antithyroid drugs and thyroxin. *J Clin Endocrinol* 1961; **21**: 7
81. Ling XW, Howe TS, Koh JS, Wong MK, Ng AC. Pre-operative thyroid dysfunction predicts 30-day post-operative complications in elderly patients with hip fracture. *Geriatr Orthop Surg Rehabil* 2013; **4**: 43–9
82. Liel Y. Rapid pre-operative preparation for severe hyperthyroid Graves' disease. *J Clin Endocrinol Metab* 2004; **89**: 5866–7. author reply 7

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