Clinical problems in thyroid surgery

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Background: Thyroid surgery is the most common endocrine surgical operation and is considered by many to be at the zenith of endocrine surgery. A good hemostasis is mandatory during a thyroid operation and many new devices have been available during the last two decades. Total thyroidectomy, (TT) is now by many surgeons considered the method of choice when treating Graves´ disease (GD) and multinodular goitres (MNG) surgically. Hypocalcaemia is the most common adverse event after thyroid surgery and the reported frequency ranges from 4-55 %. It is difficult to identify and predict patients at risk for developing postoperative hypocalcaemia. Previously described risk factors for transient hypocalcaemia are extent of surgery, lymph node dissection, GD, bone hunger and the number of parathyroid glands identified peroperatively and parathyroid autotransplantation.

Aims: To compare two different operation techniques for patients with GD undergoing TT and the risk of hypocalcaemia after TT for patients with MNG and GD, respectively. To identify risk factors for postoperative hypocalcaemia after TT in patients with GD and to predict risk factors for permanent hypocalcaemia after TT.

Methods: In Paper I we compared in a prospective randomised controlled trial, a conventional operation technique vs. ultracision (Harmonic Scalpel(HS)) when performing TT. In Paper II, we compared the risk for hypocalcaemia between patients with GD and MNG undergoing TT. In Paper III, data were extracted from the Scandinavian Quality Register for Thyroid and Parathyroid Surgery (SQRTP) and patients with GD undergoing TT during year 2004 – 2008 in 23 surgical departments in Sweden were studied. In Paper IV, risk factors of permanent hypoparathyroidism after TT from a prospective database at the same surgical department was analysed.

Results: 27 patients were randomised to the HS group and 24 patients to the conventional group (knot tying). Operation time was significantly shorter in the HS group (I). Patients with GD (n=129) were younger than patients with MNG (n=81). Symptoms of hypocalcaemia were more common in patients with GD but there were no other differences between the two groups (II). Risk factors for i.v. calcium after TT in patients with Graves´ disease were low hospital volume, operative time, university hospital and reoperation due to postoperative hematoma. Risk factors for treatment with vitamin D at discharge increased with operative time, weight of the specimen, parathyroid autotransplantation and reoperation. Risk factors for treatment with vitamin D at first follow up at 6 weeks were weight of the specimen, preoperative treatment with beta blockers. At 6 months follow up, risk factors for treatment with vitamin D were weight of the specimen and reoperation (III). There were 519 patients, median follow up (range) was 2.7 years (1.2 – 10.3). The rate of permanent hypoparathyroidism was 1.9 %. Parathyroid autotransplantation was performed in 90/519, 17.3 % and none of these developed permanent hypoparathyroidism, as did no patient with normal PTH level on day one postoperatively.

Conclusion: Patients with GD undergoing TT performed with Harmonic Scalpel® had a significantly shorter operation time, without an increased risk for complications. Patients with GD were younger and experienced more often symptoms of hypocalcaemia after TT compared to patients with goitres, but there were no biochemical differences. Risk factors for medically treated hypocalcaemia after TT in patients with Graves´ disease are multifactorial and vary over follow-up time. A low PTH level early after TT is associated with a high risk of permanent hypoparathyroidism. Normal levels of PTH postoperatively exclude long term hypoparathyroidism. Parathyroid autotransplantation seems to be warranted as a way of minimizing the risk of permanent hypoparathyroidism

Key words total thyroidectomy, Graves´ disease, multinodular goiter, transient hypocalcaemia, permanent hypocalcaemia

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Clinical problems in thyroid surgery

Páll Hallgrimsson

To my family

Ester, Einar, Birkir og Thelma

Contents

Abbreviations

FT_3	free triiodothyronine
FT_4	free (not protein bound) thyroxine
$1, 25(OH)_2D$	1,25-dihydroxyvitamin D
Ca^{2+}	serum ionized calcium
Ca	total calcium
CI	confidence interval
IQR	interquartile range
P	phosphate
PTH	parathyroid hormone
TSH	thyreotropine
MNG	multinodular goiter
GD	Graves' disease
OR	odds ratio
HS	harmonic scalpel
hr	hours
CV	coefficient of variation
TT	total thyroidectomy
ST	subtotal thyroidectomy
NT	near total thyroidectomy
PTU	propyl thiouracil
IMA	internal mammary artery
iPTH	intact parathyroid hormone
IONM	intra operative nerve monitoring
TPO	thyroid peroxidase

List of publications

Hallgrimsson P, Lovén L, Westerdahl J, Bergenfelz A. Use of the harmonic scalpel versus conventional haemostatic techniques in patients with Grave disease undergoing total thyroidectomy: a prospective randomised controlled trial.

Langenbecks Arch Surg 2008; 395: 675-680

Hallgrimsson P, Nordenström E, Bergenfelz A, Almquist M. Hypocalcaemia after total thyroidectomy for Graves' disease *and* for benign atoxic multinodular goitre.

Langenbecks Arch Surg 2012; 397: 1133-1137

Hallgrimsson P, Nordenström E, Almquist M, Bergenfelz AO. Risk factors for medically treated hypocalcemia after surgery for Graves' disease: a Swedish multicenter study of 1,157 patients

World J Surg 2012; 36: 1933-1942

Almquist M, Hallgrimsson P, Nordenström E, Bergenfelz A. Prediction of permanent hypoparathyroidism after total thyroidectomy.

In press World J Surg 2014

Introduction

Historical background

There are several historical references to diseases of the thyroid gland. In 2700 BC emperor Shen Nung (first published in Pen Tsaos, the herbals of the Chinese pharmacopoeia in1596) mentions the use of seaweed for the treatment of goitre [1]. In Indian medicine, Ayur Vedic (1400 BC until 400 AD), goitres are mentioned by the name of gala ganda and are described in detail [2]. Hippocrates (460-337 BC) stated in his book "…de become tubercular and produce struma…" Aurelius Celsus (25 BC-50 BC) was among the first to differentiate between various forms of tumour of the neck. In the western world one of the first reference is Vesalius (1514-1564) who in 1543 mentioned the thyroid gland as glandulare laryngis and considered that it produced fluid to lubricate the trachea [3]. The thyroid was also believed to have a cosmetic function in women. Back in ancient Egypt, paintings often emphasized the size of the thyroid gland in women. In the early 19th century the thyroid was thought to be a vascular shunt to divert blood flow from the brain[4]. In 1802, Giuseppe Flajani, personal physician to Pope Pius VII (1800-1823), described the association of palpitations, goitre, and bulging of the eyes. This triad was known as *Morbus Flajani* [5]. In 1820 Rush reported that the thyroid gland was larger in women because it is " necessary to guard the female system from the influence of the more numerous causes of irritation and vexation of mind to which they are exposed than the male sex " [3]. The association between thyroid enlargement and the characteristic clinical features of hyperthyroidism was not recognized until 1786, by Parry [6]. The publication of Parry was followed by the classic description of thyreotoxicosis by Graves [7] and von Basedow [8] in 1835 and 1840 respectively. Graves´ disease (GD) owes its name to the Irish doctor Robert James Graves who described a patient with goitre and exophthalmus in 1835. Karl Adolph von Basedow independently reported the same constellation of symptoms in 1840. As a result, in continental Europe, the terms Basedow's syndrome, Basedow's disease or Morbus Basedow are more common than Graves´ disease. However, according to some sources, the Persian physician Sayyid Ismail Al-Jurjani noted the association of goitre and exophthalmus more than eight hundred years ago in *Thesaurus of the Shah of Khwarazm*, the most famous of his five books, and the major medical dictionary of its time [9].

Anatomy and embryology of the thyroid gland

The word thyroid originates from the Greek word thyreos meaning shield. The term thyroid was first used by Thomas Wharton (1614-1673). He named the thyroid '*Glandular thyroideis*' in 1656 [10]. Embryologically, the thyroid gland develops approximately 24 days after gestation from endodermal epithelial cells on the median surface of the pharyngeal floor – the foramen cecum. The thyroid has a double origin: the primitive pharynx and the neural crest. Fig.1.
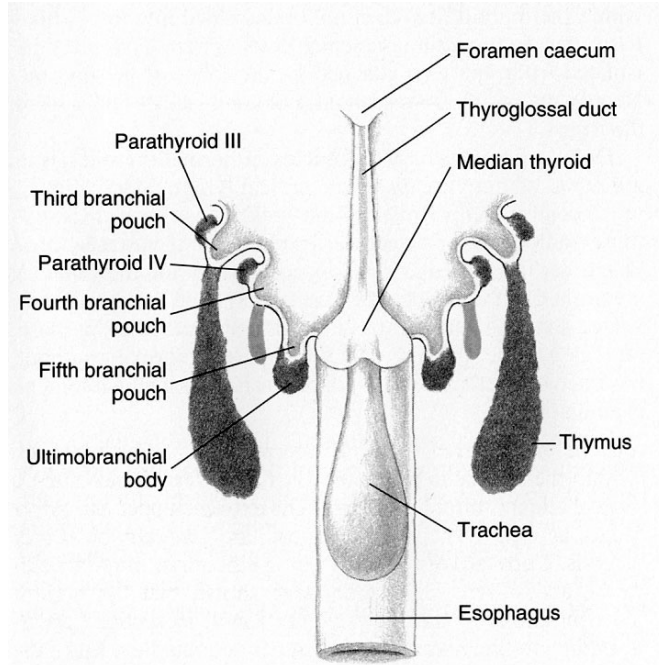
Figure 1. Schematic view of the primitive pharynx of an 8 – 10 mm embryo. Printed with permission.

The primitive pharynx is the origin of the medial thyroid anlage, whereas the lateral thyroid anlage originates from neural crest, which is also the source of the parafollicular cells or C-cells that secrete calcitonin. The thyroid develops caudal to the median tongue bud, which arises from the first pharyngeal arch and rostral to the copula, and develops from the second pharyngeal pouch. By the seventh gestational week, the thyroid gland descends anterior to the hyoid bone, thyroid cartilage, and cricoid cartilage, to rest anterior to the trachea. The path of descent is marked by the thyreoglossal duct, a tubular structure of thyroid tissue that usually obliterates completely between the 7th and 10th gestational week [11]. Fig 2.

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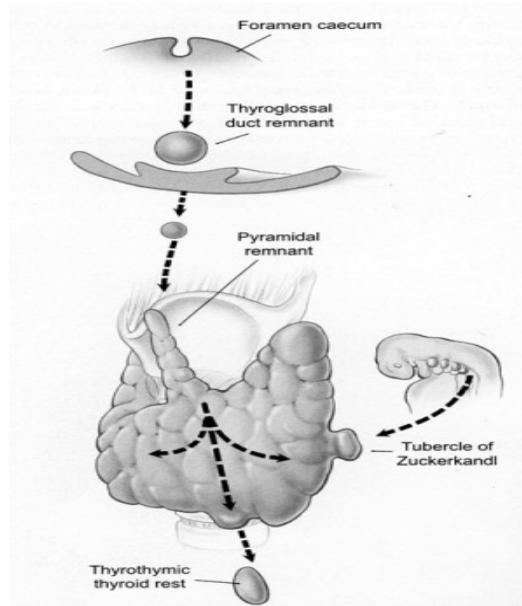
Figure 2. Schematic view of ectopic sites of thyroid tissue. The anatomical and pathological findings related to embryological development. Printed with permission.

The fully developed thyroid gland is composed of two lateral lobes and a central isthmus with or without a pyramidal lobe. The thyroid is invested in the middle layer of the deep cervical fascia and is attached from its superior-medial aspect to the thyroid and cricoid cartilage via the anterior suspensory ligament. The ligament of Berry (the posterior suspensory ligament) connects the posterior-medial aspect to the first and second tracheal ring and the cricoid cartilage. The tubercle of Zuckerkandl comprises the posterior and lateral aspect of the thyroid lobe [12, 13]. The thyroid gland is a highly vascular structure. The major arterial contributors are the superior thyroid artery, a branch off of the external carotid artery, and the inferior thyroid artery, which is a branch of the thyreocervical trunk. The internal mammary artery provides an arterial supply to the inferior border of the isthmus in 2-12 per cent of patients. Venous drainage is through the superior, medial and inferior veins which drain into the internal jugular veins or the innominate veins. Lymphatic drainage tends to follow the veins drainage. The gland is innervated by the superior, middle and inferior cervical ganglia of the sympathetic trunk, as well as by parasympathetic fibres from the vagal nerve. The thyroid gland primarily regulates body metabolism. The thyroid gland secretes two main thyroid hormones – thyroxine (T4) and triiodothyronine (T3). In order to produce T3 and T4, the thyroid gland is dependent on iodine. The T4 and T3 hormones stimulate to the production of proteins in various tissues and increase the amount of oxygen used by cells. The secretion of T3 and T4 by the thyroid is controlled by a feedback mechanism which involves the Pituitary gland and the Hypothalamus.

Fig 3. The hormone calcitonin is also produced by the thyroid gland. This hormone, secreted by a small population of cells known as C cells, is involved in the regulation of calcium metabolism. The most prominent factor controlling the secretion of calcitonin is the extracellular concentration of ionized calcium.
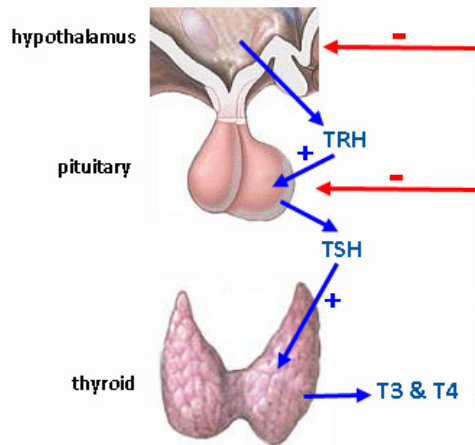
Figure 3. Function of the thyroid gland. The synthesis and release of the thyroid hormones is regulated by negative feedback involving the pituitary hormone. Printed with permission.

Graves´ disease

Graves' disease (GD) is a disorder of the immune system that results in the overproduction of thyroid hormones (hyperthyroidism). Graves' disease is the most common cause of hyperthyroidism and is caused by the production of auto antibodies to the thyroid stimulating hormone (TSH, thyreotropin) receptor (TSHR-AB). The TSHR-AB activates the receptor, thereby stimulating thyroid hormone synthesis and secretion as well as thyroid growth. The presence of TSHR-AB in serum, and exophthalmus on clinical examination, distinguishes the disorder from other causes of hyperthyroidism. The thyroid gland is usually, but not always, diffusely enlarged. The histology of the thyroid gland in patients with GD is characterized follicular hyperplasia, intracellular colloid droplets, cell scalloping, a reduction in follicular colloid and a patchy (multifocal) lymphocytic infiltration. The histological picture may be influenced by treatment with anti-thyroid drugs [14]. The diagnosis of GD is made by physical examination and blood tests (TSH, T4 and T3 and TSH antibodies, TPO antibodies). Ultrasound and radioiodine uptake is of value in the work-up in patients with symptoms of GD but with negative antibodies. The prevalence of GD in children

in Sweden is about 1/100 000 child/year. Graves´ disease is uncommon before puberty but during puberty the prevalence increase to 3/100 000 child/year. The general incidence of hyperthyroidism in Sweden (27.6/100 000 inhabitants), is in the lower range compared with earlier international reports. Seventy-five percent of the patients with hyperthyroidism have GD and 20 per cent of patients with GD have thyroid-associated ophthalmopathy. The female to male ratio is 3.9:1. [15]. Treatments of GD focus on controlling the hypersecretion of thyroid hormones. Clinical symptoms like rapid heart rate, sweating and anxiety, are treated with beta-blockers such as propranolol until hyperthyroidism is controlled. Hyperthyroidism may be treated with:

- Antithyroid medications
- Radioactive iodine
- Surgery

Goitre

The term goitre simply refers to the abnormal enlargement of thyroid gland. The presence of a goitre does not necessarily mean that the gland is malfunctioning. A goitre can occur in a gland that secretes too much hormone (hyperthyroidism), too little hormone (hypothyroidism), or correct amount of hormone (euthyroidism). One of the most common causes of goitre worldwide is iodine deficiency [16]. However iodine deficiency is nowadays rather uncommon in many, albeit not all parts, of the western world. Multinodular goitre (MNG) is the most common cause of enlargement of the thyroid gland. Individuals with this disorder have one or more nodules within the gland which causes thyroid enlargement [16]. Patient can present with a single large nodule or with multiple smaller nodules in the gland. The cause of MNG is not well known. About 5-10 per cent of the Swedish population has a palpable nodule in the thyroid gland and about 50 per cent of the population has a nodule in the thyroid gland when investigated by ultrasound. Multinodular goitre is more common in women than men, and the prevalence increases with age [17]. The diagnosis of a goitre is made by physical examination, ultrasound, and blood tests to rule out aberrations in thyroid hormone secretion, and fine needle aspiration to exclude malignancy. Computer tomography is valuable in patients with retrosternal goitres.

Embryology and anatomy of the parathyroid glands

Normally there are four parathyroid glands, but several autopsy studies have reported that 3-6 per cent of the population have fewer than four parathyroid glands. More than four glands occur in 2.5-6.7 per cent [18-20]. The parathyroid glands vary considerably in size, shape, number and location, and therefore represent a unique challenge during thyroid and parathyroid surgery. The parathyroid glands develop from the third and fourth pharyngeal pouches. The inferior parathyroid glands develop from the third pouch and descend at week 7 after gestation with the thymus to eventually rest at the dorsal surface of the thyroid gland outside of the thyroid capsule. The superior parathyroid glands develop from the fourth pouch and descend with the thyroid gland. The superior parathyroid glands are usually posterior to the inferior glands, and usually lie posterior to the plane of the recurrent laryngeal nerve. Because of the longer embryological migration of the inferior glands, they are more widely distributed anatomically, and more likely to be in an ectopic position than the superior glands. The vascular supply of the parathyroid glands is usually derived from the inferior thyroid artery, but early anatomical studies have claimed that there are branches from the superior thyroid artery which supplies the superior glands. It has been established that up to 40 -45 per cent of parathyroid glands have a distinct anastomosing branch between the superior and inferior thyroid arteries. One third of the parathyroid glands have two or more parathyroid arteries [21, 22].

The parathyroid glands and calcium metabolism

Calcium is the most abundant mineral in the body. The average adult contains approximately 1 kg (25 000 mmol) of calcium and 99 per cent is bound to the skeleton. The total calcium content in the extra cellular fluid is about 22.5 mmol, with about 9 mmol in the plasma. In the plasma, calcium is present in three forms; bound to protein (mostly albumin), as a complex with citrate and phosphate, and as free ions. Only the latter form is physiologically active and it is the concentration of ionized calcium which is maintained by haemostatic mechanisms. The most commonly used methods for determining plasma calcium concentration is to measure total calcium encompassing the protein bound and ionized fractions. Calcium is mainly bound to albumin. Any disorder that alters the concentration of plasma albumin will affect total calcium independently of the ionized calcium concentration. This may lead to possible misinterpretation of results in both hypoproteinaemic and hyperproteinaemic patients. Thus, it is preferable to measure the biologically active ionized calcium concentration. Binding of calcium to albumin and others anions increases in alkalosis, therefore blood samples need to be adjusted to normal ph (e.g., ph 7.4). [23, 24]. The ionized fraction

of calcium remains stable throughout life but total calcium usually decrease with age due to an age-related decrease in serum albumin concentration [25]. Regulating hormones for calcium metabolism are mainly parathyroid hormone (PTH) and 1,25 dihydroxycholecalciferol. Parathyroid hormone is produced by the parathyroid glands, and is a single peptide chain consisting of 84 amino acids. The final hormone has a molecular weight about 9500 D and is discharged by exocytose from chief cells of the parathyroid gland. The control of PTH secretion is predominantly regulated by the extracellular calcium concentration through a specific Ca 2+ sensing receptor on the surface of the parathyroid gland[26]. Parathyroid hormone acts throughout the body to increase the concentration of ionized calcium. PTH increases gastrointestinal absorption through activation of 25-hydroxy- cholecalciferol ($25(OH)D_3$) to the more active vitamin D 1,25 ($1,25(OH)_2D_3$) in the kidney, which in turn increases gut absorption of dietary calcium. Through feedback, the activated vitamin D decreases the synthesis of PTH from the parathyroid gland and stimulates calcium transport in bone and intestinal tissue; it also increases calcium reabsorption in the kidney. Serum ionized calcium inhibits the production of PTH from the parathyroid glands at elevated levels. If the parathyroid glands have been injured, they may not respond appropriately to low ionized calcium levels [27]. Fig.4.
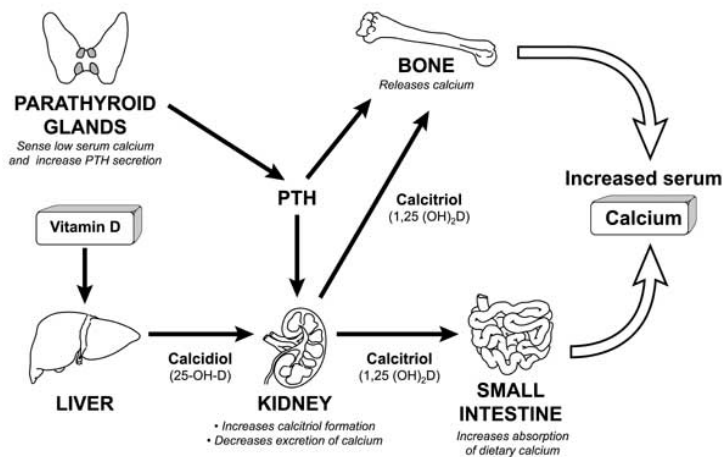
Figure 4. Overview of calcium metabolism and target organs.

The recurrent laryngeal nerve

Anatomy

Galen of Pergamon (AD 129-1999) was the first anatomist to describe the recurrent laryngeal nerve (RLN) as a branch of a cranial nerve and Andreas Vesalius (1555) was the first to make drawings of the cranial nerves and their branches. Willis (1621-1675) described the vagal nerve and the RLN as found in most modern text books [28]. The anatomic course of the recurrent laryngeal nerve is variable. The recurrent laryngeal nerve branches off the vagal nerve and is present by the sixth gestational week, associated with the sixth branchial arch. The aortic arches are cranial to the larynx at this stage, and therefore, the nerve does not loop at this point. As a result during embryonic lengthening of the neck, the larynx moves cephalad and the RLN moves with it. Although the distal portion of the sixth aortic arch degenerates on the right, it persists on the left as the ductus arteriosus. The left RLN stays below the ductus arteriosus and ascends to the larynx [11, 12]. A non-recurrent laryngeal nerve occurs in approximately one per cent of the population, when the right nerve enter larynx directly without forming a loop. The right RLN enters the neck base at the thoracic inlet more laterally than the left RLN does. At the paratracheal region, the right RLN tends to travel obliquely before entering the trachea at an angle of between 15 -30 degrees.[29]. Fig. 5
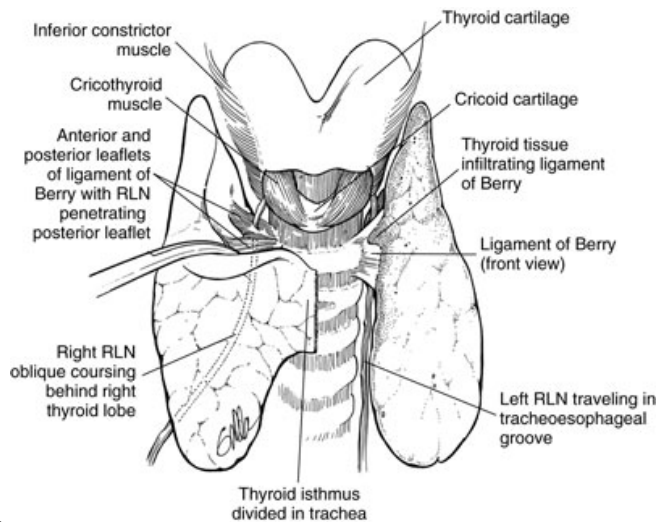
Figure 5. Front view of thyroid gland and larynx, showing the course of the recurrent laryngeal nerve through the ligament of Berry. Printed with permission.

Function of the recurrent laryngeal nerve

The recurrent laryngeal nerves controls all intrinsic muscles of the larynx except for the cricothyroid muscle, which is innervated by the external branch of the superior laryngeal nerve. The intrinsic laryngeal muscles are responsible for voice control. Notably, the only muscle capable of separating the vocal cords for normal breathing is the posterior cricoarytenoid. If this muscle is incapacitated on both sides, the inability to pull the vocal folds apart (abduct) will cause difficulty in breathing. Therefore, bilateral injury to the recurrent laryngeal nerve will cause this condition. The nerves also convey sensory information from the mucous membranes of the larynx below the lower surface of the vocal fold [30].

Thyroid surgery

History of thyroid surgery

Thyroid surgery has been performed since ancient times. Abu al-Qasim, Islam´s legendary medieval surgeon, is credited with performing the first goitre excision in which the patient just avoided exsanguinations, as recorded in his surgical tome, *Al-Tasrif*, in 952 AD [31]. In 1st century AD, Celsus reported that the removal of such a mass was dangerous in the Roman encyclopedia. Albucasis, the 11th century surgeon of Corodoba, also described extirpation of the thyroid gland. The surgeons of Salerno in 12th century were transfixing large goitres with Setons, e.g. threads passed through the mass to produce suppuration. They also treated the patients with seaweeds, either dried or burned, and these methods were published by Roger Frugardi in 1170. Technical improvements did not occur until the middle of the 19th century. In the interim period, appalling results of thyroid surgery led in 1646 to the imprisonment of a surgeon and to a total ban on thyroid surgery by the French academy of medicine in 1850.

The first documented partial thyroidectomy was carried out by Pierre Joseph Desault in 1791. He removed a four cm mass from the thyroid through a vertical incision, tying the superior and inferior thyroid arteries and then dissecting the gland from trachea. Thyroid surgery as well as medical treatment of thyroid diseases remained in its infancy until the second half of the 19th century. The discovery of iodine in burned ash of seaweed in 1811 led to successful treatment of some goitres [32]. Thyroid surgery came of age because of new developments in medicine such as the use of ether anaesthesia in 1846, antisepsis in 1867 and the first effective artery forceps in 1870. These developments allowed unhurried and safe dissection [33]. According to Dr. S. Alam Hannan [31] the magnificent seven in the history of thyroid surgery are: Theodor Billroth (1829-1894), Theodor Kocher (1841-1917), William Halsted (1852-1922),

Charles Mayo (1863-1939), Georg Crile (1864-1943), Frank Lahey (1880-1953), and Thomas Dunhill (1876-1957)
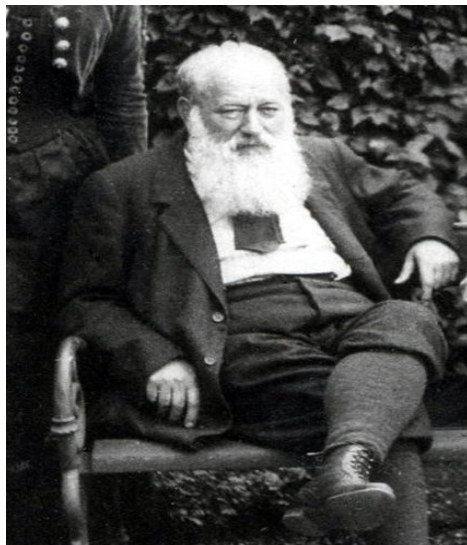
Figure 6. Theodor Billroth
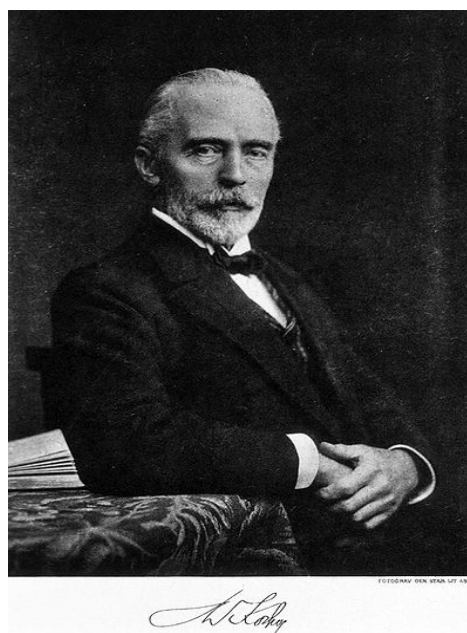
Figure 7. Theodor Kocher

All the above surgeons contributed to make thyroid surgery safer and more efficient. However, it is Theodor Kocher who generally is credited with the most important contribution within the field, and thus has been called the father of thyroid surgery. Theodor Kocher was the first surgeon to receive the Nobel Prize in Medicine and Physiology in 1909 for his life work in understanding thyroid diseases through surgery and research [31].

Instruments in modern thyroid surgery

Conventional haemostatic techniques in thyroid surgery have for many years included knot tying. During the years, surgical instruments have been refined. New instrument haves been introduced to general surgery as well as to thyroid surgery to lower the risk of complications and shorten operation time.

Diathermy

The term "diathermy" is of Greek origin (dia; through, thermy; heat). Diathermy is a method whereby a high frequency electric current, usually within the range of 300 – 3000 kHz, passes through the tissue. The most widely used function of diathermy is to achieve haemostasis during a surgical procedure. Uni - or monopolar diathermy is employed in most surgical procedures by using two separate electrodes connected to the terminals of an electrical generator. In this way the current passes through the body of the patient. Bipolar diathermy is used in more delicate surgical procedures and is often used solely for haemostatic purposes and not to cut or dissect. The electrical current passes through the instrument but not the patient[34, 35]. Fig. 8.

Figure 8. Mono-and bipolar diathermy. Different types of bipolar forceps and scissors.

Ultracision

The Harmonic Scalpel (HS) is a cutting instrument used during surgical procedures to cut and coagulate tissue and vessels up to 5 mm in diameter. The instrument was first introduced in thyroid surgery in 1998. The instrument is superior to bipolar diathermy in that it can cut through thicker tissue, creates less toxic smoke, and may offer greater precision [36, 37]. The shaft of the HS vibrates at the frequency of 55 kHz when dividing the tissues. The high frequency vibration of tissue molecules generates stress and friction in tissue, which produces heat and causes protein denaturation. The technique infers that minimal energy is spread to surrounding tissue preventing collateral damage. The power settings can be adjusted to different levels in order to control the speed of cutting and coagulation [38]. The Harmonic brand is manufactured and distributed by Ethicon Endo-Surgery a subsidiary of Johnson & Johnson. Fig. 9.

Figure 9. Ultracision® Harmonic Scalpel, Focus.

Ligasure

The LigaSure™ vessel sealing system, is an isolated output electrosurgical generator that provides power for vessel sealing and bipolar surgery. The LigaSure vessel sealing system provides precise energy delivery and electrode pressure to vessels for a controlled time period, and thus achieves a complete and permanent fusion of the vessel lumen. This system works on isolated arteries and veins up to 7 mm in diameter and tissue bundles. The latest model "Ligasure small jaws" is able to seal and coagulate vessels and cutting as well. Two modes are available:

- Bipolar – for most applications. The system provides low voltage to prevent sparking. The power remains constant over a specific range of tissue impedance, allowing a consistent tissue effect.
- Macrobipolar – for bipolar cutting or rapid coagulation. The system provides higher voltage and greater power than with the bipolar mode. [39].

LigaSure has been used since 2003 [40].

LigaSure Vessel Sealing Generator Service Manual, Manufactured by Valleylab, a division of Tyco Healthcare Group LPBoulder, Colorado 80301-3299 USA Made in USA Printed in USA; ©2008 Valleylab: All rights reserved. Fig. 10.

Figure 10. Ligasure, small jaw instrument.

Biclamp

BiClamp® uses a high-current low-voltage electrical energy that is auto-regulated to prevent the excessive thermal damage and scarring of tissues that occurs with conventional electro cautery devices. Effective coagulation and fusion of vessels up to 7 mm is possible with BiClamp. The BiClamp instruments can be sterilized and is therefore reusable which potentially decreases costs compared with instruments such as Ultracision Harmonic Scalpel and Ligasure. (ERBE Elektromedizin GmbH; http://www.erbe-usa.com). Fig. 11.

Figure 11. Biclamp, electrosurgical coagulation.

Total thyroidectomy

The surgical management of GD and multinodular goiters (MNG) has been controversial over the years. Some authors support total thyroidectomy and others subtotal thyroidectomy (ST) leaving approximately 3-4g remnant thyroid tissue on one or both sides (Hartley-Dunhill; Enderlen-Hotz producers respectively), or near total thyroidectomy (NT) leaving approximately 1 g thyroid tissue in situ. All above procedures have been utilized for almost 100 years. Recent studies support total thyroidectomy as the treatment of choice for GD and MNG, because of the risk of recurrent disease when leaving tissue remnants [41-44]. Contemporary thyroid surgical procedures are mostly done under general anaesthesia, even though operations have been performed under hypnosis and local anaesthesia [45]. Total thyroidectomy in patients with benign thyroid diseases is performed by a transverse incision in the neck, originally introduced by Theodor Kocher in 1890, and hence often called a Kocher incision. After dividing the subcutaneous fat and the platysma muscle, the straight muscles (mm. sternothyroideus, sternohyoideus) are retracted laterally to get access to the thyroid gland. The thyroid gland is highly vascularised organ, and therefore it is important to achieve good haemostasis during surgery. Full mobilization of thyroid gland is achieved by dividing the superior and the inferior vessels by ligation or by the newer instruments for coagulation. When dividing the superior pole vessels it is of importance to identify the external branch of the superior laryngeal nerve. This nerve is usually found on the inferior pharyngeal constrictor before entering the cricothyroid muscle. Early in the procedure, the RLN is identified; most departments are nowadays familiar with intraoperative nerve monitoring by EMG to minimize the risk of surgical trauma to the nerve during dissection. The parathyroid glands are identified without unnecessary dissection which may cause devascularisation and disturb parathyroid function. If traumatic injury to the parathyroid glands is noticed during operation, the parathyroid gland is divided into small pieces (approximately one mm^3) and auto transplanted into the sternocleidomastoid muscle.

Complications to thyroid surgery

Total thyroidectomy is the most commonly performed endocrine operation, and most patients recover fully without any adverse events [46]. However sometimes complications may result, and the most common complications are hypocalcaemia, paresis of the RLN, postoperative bleeding, infection and lymph leakage - the latter is predominantly seen in surgery for malignancy.

Postoperative Hypocalcaemia

The most common complication after total thyroidectomy is hypocalcaemia. Traditional methods for detecting hypocalcaemia in the postoperative period include frequent monitoring of total and ionized calcium levels as well as close clinical monitoring for symptoms of hypocalcaemia. The prevalence of hypocalcaemia, using the most common definition (total serum calcium < 2 mmol/L on the first postoperative day), ranges from 16 to 55 per cent [47]. Well known risk factors for transient hypocalcaemia are the extent of surgery (total thyroidectomy vs. subtotal- or near total thyroidectomy), lymph node dissection, per operative haemodilution, thyreotoxicosis, postoperative bone calcium reabsorbtion (so called "bone hunger") and the number of parathyroid glands identified during surgery and left in situ [48-50]. Symptoms usually appear 24 - 48 hours after surgery and it is notoriously difficult to predict which patients that will develop hypocalcaemia. The clinical manifestations of hypocalcaemia range from neuromuscular irritability such as paraesthesia and numbness of the fingertips and the perioral area to muscle cramps

Twitching of the ipsilateral facial musculature (perioral, nasal, and eye muscles) by tapping over cranial nerve VII at the ear, is known as Chvostek's sign. Contraction at the oral angle alone is seen in 10 to 25 per cent of the normal population. Trousseau's sign consists of carpal spasm provoked by ischemia induced by inflation of a blood pressure cuff around the arm, or alkalosis, provoked by hyperventilation. Spontaneous muscle cramps are commonly seen in hypocalcaemia. Hypocalcaemia leading to prolonged contraction of the respiratory and laryngeal muscles may cause stridorous breathing and cyanosis [51].

Hypoparathyroidism is defined as an insufficient level of PTH leading to lower than normal levels of calcium. Transient hypoparathyroidism is usually defined as a condition lasting less than one year, and permanent hypoparathyroidism lasting one year or longer [52]. Recent studies investigating early predictive factors of hypocalcaemia after total thyroidectomy, report that intact PTH (i PTH) levels may predict hypocalcaemia [53]. The utility of PTH in detecting postoperative hypocalcaemia has been discussed controversially, but at present, there is only one international recommendation. The Australian Endocrine Surgeon Society recommends the measurements of PTH in evaluating postoperative hypocalcaemia[54]. Nevertheless, the best timing, measurement and test methods for i-PTH remain controversial [55-57].

Most surgeons consider total thyroidectomy due to GD the most challenging thyroid surgical procedure. It has also been reported that patients with GD have higher risk of postoperative hypocalcaemia compared with other indications for thyroid surgery [58-60]. The reasons for this increased risk are not clear, but may be due to increased vascularisation of the thyroid gland. Further, the autoimmune inflammation of the thyroid gland may cause more difficulty in the identification of the parathyroid glands

with challenging dissection, and a higher risk of damage. The higher incidence of hypocalcaemia seen after surgery for GD could also be due to the influence of thyroid hormones on calcium metabolism. Increased levels of thyroid hormones accelerate bone formation and remodelling, and a decrease of thyroid hormones after total thyroidectomy results in an alteration of the calcium balance, leading to "bone hunger" [61].

Paresis of recurrent laryngeal nerve

One of the most important complications after thyroid surgery is injury to the recurrent laryngeal nerve (RLN). Damage to RLN results in a paresis of the sole abducting muscle of the vocal cord, the posterior cricoarytenoid muscle.. Injury of the RLN may cause symptoms ranging from almost no symptoms to hoarseness in unilateral paresis, and stridor and acute airway obstruction in bilateral paresis [62]. The proposed mechanism in which thyroid surgery may result in vocal cord paralysis includes complete or partial transaction of the nerve, distension or stretch of the nerve, compression, oedema, ischemia, perineural fibrosis, calcification and toxic neuritis [63]. The incidence of transient paresis of the RLN after thyroid surgery varies from 1 – 13 per cent [64, 65], depending on centre and indication for surgery. Permanent paresis of RLN occurs in approximately 0 – 3 per cent of patients [66]. Treatment of unilateral RLN paresis is aimed to eliminate aspiration and improve voice. Objective voice analysis assessment and therapy by a speech-therapist is helpful in virtually all patients who have dysphonia. The two main surgical options for patients who have permanent unilateral RLN paresis are medialisation of the vocal cord or nerve reinnervation, e.g., restoration of the nerve either spontaneously or by surgical nerve grafting. [66].

Postoperative bleeding

Postoperative bleeding after thyroid surgery is a feared and life-threatening complication and occurs in less than 2 per cent of thyroid and parathyroid procedures.[67, 68]. Although total thyroidectomy is a common procedure, postoperative bleeding after thyroid surgery is fortunately a rare event. Postoperative haemorrhage may occur immediately after the operation and up to several days postoperatively. However, the majority of the hematomas occur within 24 hours after surgery. An international multi-centre study found that a significant number of patients returned to the operating theatre for evacuation of hematoma after more than six hours after thyroidectomy. The use of drains, operation for GD, benign histology, the use of antiplatelet or anticoagulation medications, as well as increased specimen weight were independent risk factors associated with hematoma after thyroidectomy [69]. Other studies have shown, however, that postoperative hematoma and haemorrhage are no different in patients with or without drains [70, 71]. Deep hematomas may cause respiratory distress and airway compression, and when recognized should be relieved

immediately; the wound should be opened and the hematoma evacuated. When in doubt concerning intraoperative haemostasis, a cellulose based haemostatic agent or microfibrillar collagen may be useful as an adjunct to haemostasis [72-74].

Wound complications

Wound complications such as infection, seroma, and hypertrophic scarring/keloid formation, are uncommon after thyroid surgery. Seroma formation after thyroid surgery is uncommon and occurs in 1to 6 per cent of patients [75, 76]. The risk of seroma increases with the extent of surgery (bilateral surgery) or thyroidectomy for large goitres [77]. Seroma management is often conservative; the fluid will gradually resolve but may induce a slight discomfort for the patient. Wound drainage does not significantly reduce the incidence of postoperative seroma formation [78].

In general, the neck is a clean area and the routine use of perioperative antibiotics has not proven to be beneficial. Postoperative infection occurs in 1-2 per cent after thyroid surgery. Superficial infection (cellulitis) should be treated with antibiotics. Deep infections are managed with incision and drainage and intravenous antibiotics. The use of drains has been associated with increased risk of postoperative infection. [79, 80].

Aims of the thesis

- To compare two different operation techniques for patients with Graves´ disease undergoing total thyroidectomy

- To investigate the risk of complications for patients with benign atoxic multinodular goitre and patients with Graves´ disease after total thyroidectomy

- To identify risk factors for postoperative hypocalcaemia and hypoparathyroidism after total thyroidectomy in patients with Graves´ disease

- To predict risk factors of permanent hypoparathyroidism after total thyroidectomy

Methods

Study 1

Patients

Between November 2003 and May 2006, patients with the preoperative diagnosis of GD referred for surgery to the Department of Surgery, Lund University Hospital and Kristianstad Central Hospital, respectively, were included in the study after oral and written consent.

All patients were treated preoperatively with thyreostatics and were euthyroid prior to operation. Besides standard blood tests for thyroid function (TSH, T4, T3), preoperatively laryngoscopy was performed in all patients.

Randomization

Randomization was carried out by the use of consecutively numbered opaque and sealed envelopes in blocks of five to either total thyroidectomy with the use of Ultracision° Harmonic Scalpel (HS) (Ehticon Endo Surgery, Cinncinati, OH, USA) or total thyroidectomy with conventional haemostatic techniques. In the conventional group, mono- and bipolar coagulation, as well as ligatures and clips, were allowed.

Surgery

All patients were operated under general anaesthesia with endotracheal intubation. A standard Kocher incision, 4 – 6 cm in length, was made over the central neck. Intraoperative bleeding was estimated by weighing the gauzes before and after use. One gram was thereby estimated to be equal to one millilitre of blood. Operation time (skin - to -skin) and the time for anaesthesia were recorded. The patients were blinded to the allocated study group. Blinding to surgeons was not possible.

Study endpoints

The primary end point of the study was operative time and secondary end points were per-operative bleeding, complications and costs. Operation time and the time for anaesthesia were recorded. Costs calculations were made for direct costs for the two procedures such as different equipment's and operation time. At the time of the study the operating room costs was approximately € 4.5 per min of anaesthesia (€1 = SEK 9,

27; May 31 2006). All patients were followed at four weeks and at six months. The study end-points were analysed on an intention - to - treat basis.

Follow-up

Plasma levels of total calcium were measured on the first postoperative day. The need for oral substitution with calcium and/or vitamin D during hospital stay and at patient discharge was recorded together with complications. Serum total thyroid hormone concentration and serum levels of total calcium were measured at follow up after 4 weeks and at six months. Postoperative laryngoscopy was performed within four week after surgery in all patients.

Statistical analysis

On the basis of previous studies, it was calculated that with an α error of 0.05 (two sided) and a power of 0.80, twenty five patients in each arm were needed to find a difference of 25 minutes in operative time between the two groups of patients. Continuous variables are presented as median (range) if not stated otherwise. Categorical data are presented as numbers and per cent. Differences between groups were analysed by the Mann-Whitney U test, Kruskal-Wallis test, chi-squared test (X^2), and by Fisher´s exact test when expected frequencies were less than five. $P<0.05$ was considered significant.

Study 2

Patients

Between January 1999 and October 2009 data on patients with GD and patients with MNG undergoing primary operation with total thyroidectomy at Lund University Hospital, were entered in a database. Pre- and postoperative levels of total calcium and plasma levels of PTH as well as symptom and signs of hypocalcaemia (perioral numbness, tingling in feet and hands, muscle cramps, paraesthesia), were recorded. Oral calcium and vitamin D were supplemented liberally on demand, a decision made by the attending doctor based on patients' biochemistry and/or symptoms. Intravenous calcium was given to patients with severe symptoms (muscle cramps). Prior to surgery all the patients with GD were treated with thyreostatics at least for three months and were euthyroid,

Surgery

All patients were operated on under general anaesthesia. The numbers of parathyroid glands detected during operation were recorded, and if accidentally removed or devascularised, they were cut in small pieces of approximately 1mm^3 in volume and

auto transplanted. All patients were operated by endocrine surgeons performing more than 50 thyroid procedures annually.

Follow-up

At discharge and at six weeks and six months follow-up, medication with calcium supplements and vitamin D were documented. Serum levels of total calcium and plasma levels of PTH were analysed and recorded. Patients treated with vitamin D analogue therapy at six months follow-up, were considered to have permanent hypoparathyroidism.

Biochemical variables

Serum total calcium (reference range: 2.15 – 2.50 mmol/L) was measured with routine methods on a Hitachi 917, with a coefficient of variation (CV) of 2.0 per cent at 2.40 mmol/L. PTH was analysed by an assay for intact PTH (Hitachi Modular-E) (reference range: 1.6 – 6.9 pmol/L). The threshold for detection was 0.7 pmol/L. The analysis of PTH has a total CV of 5.9 per cent at 7 pmol/L and 5, 9 per cent at 100 pmol/L.

Statistical analysis

Data analysis was performed with Statview 5.01 (Abacus Concept, Berkeley, CA) and SPSS v 19.0 (SPSS, IBM Corporation, Somers, NY). Values are expressed as numbers (percent) and medians (interquartile range, IQR). For continuous variables group differences were analysed by Mann Whitney U test. For the nominal variables the chi2 test was used or the Fischer exact test when the expected frequency was less than five. All tests were two sided. A multivariable logistic regression was fitted including variables available from the dataset that were considered to biologically relevant for post-operative hypoparathyroidism and presented as odds ratio (OR) and 95 per cent confidence interval (CI). Included variables were; age, gender, preoperative levels of total calcium and PTH, the number of intraoperatively identified parathyroid glands, and the number of auto transplanted parathyroid glands, and the indication for surgery (GD or MNG). Analysed outcomes were symptoms of hypocalcaemia in the immediate postoperative period, biochemical hypocalcaemia (total calcium > 2,00 mmol/L) on postoperative day 1, calcium and Vitamin D supplementations at discharge, and at follow up after sixweeks. A p-value of <0.05 was considered significant.

Study 3

Patients

Data were extracted from the Scandinavian Quality Register for Thyroid and Parathyroid Surgery (http://www.thyroid-parathyroidsurgery.com), an online web-based database for quality control in thyroid and parathyroid surgery. The database was launched 2004, and is recognized by the Swedish National Board for Health and Social Welfare as the national quality registry within the field. The database is open to all surgical departments within Scandinavia.

Patients with GD undergoing total thyroidectomy during year 2004 - 2008 in 23 surgical departments in Sweden were studied. In the present study, hypocalcaemia was defined as treatment with calcium and/or vitamin D.

Variables

Variables extracted from the register are shown in Figure 2

Preoperatively	Type of department(university vs. non-university), gender, age, serum levels of total calcium, medical treatment and presence of endocrine ophthalmopathy, results of preoperative larayngoscopy
Perioperatively	Type of operation, simultaneous surgery due to hyperparathyroidism, number of identified parathyroid glands, auto transplantation of parathyroid tissue, operative time and weight of the specimen
In ward and at discharge	Serum levels of total calcium on postoperative day 1, medication with i.v. or oral calcium, and/or Vitamin D due to biochemical or symptomatic hypocalcaemia, bleeding with reoperation and postoperative wound infection
At six weeks and six months	Serum levels of total calcium, medication with oral calcium and/or Vitamin D due to hypocalcaemia, and results of postoperative laryngoscopy

Figure 2 Variables extracted from the registry for the present study.

The influence of hospital volume of thyroid surgery on outcome were evaluated by the number of thyroid operations performed during 2008 in Sweden according to official statistics published by Swedish National Board for Health and Social Welfare. To estimate the influence of teaching hospital, departments were classified as university and non-university departments.

Follow-up

Follow-up was performed after six weeks. A further follow-up was performed at six months for those patients that were treated due hypocalcaemia with oral calcium and/or vitamin D at the six week follow-up.

Results are presented as median and interquartile range (IQR) for continuous variables if not stated otherwise, and as number and percent for nominal variables. For statistical evaluation of difference between groups, the Mann Whitney U test was used for continuous variables and Fischer´s exact test was used for the nominal variables. To estimate odds ratio (OR) a uni- and multivariable logistic regression analysis were used with 95 per cent confidence interval (CI), a p-value < 0.05 was considered significant. All tests were two sided.

Study 4

Patients

Data was extracted from a local database held in accordance with legislation contained in the Personal Data Act, on patients treated with total thyroidectomy 1991-2011.

Analysed variables and follow-up

Indications for surgery, pre – and postoperative levels of calcium and parathyroid hormone (PTH), as well as medication with calcium or vitamin D supplements were routinely recorded during the hospital visit, at discharge and at follow up after one month and six months or later if necessary. Calcium and vitamin D was supplemented on demand and stopped as soon as possible. Indications for surgery were classified into three groups: thyrotoxicosis, non-toxic benign goitres and malignancy. Patients unable to cease either calcium or vitamin D at six months were followed for at least a further six months, with blood tests for analysis of PTH and total calcium if necessary. Serum levels of PTH were measured immediately after surgery and on day 1. A greater proportion of patients had missing values of PTH immediately after surgery than day 1. Because there was a good correlation between PTH levels at day 1 and directly after surgery, a missing PTH value on day 1 was replaced by the PTH value immediately after surgery.

Permanent hypoparathyroidism, defined as inability to cease vitamin D at one year or earlier

Biochemical variables

Serum total calcium (reference range: 2.15 – 2.50 mmol/L) was measured with routine methods on a Hitachi 917, with a coefficient of variation (CV) of 2.0 per cent at 2.40 mmol/L. PTH was analysed by an assay for intact PTH (Hitachi Modular-E) (reference range: 1.6 – 6.9 pmol/L). The threshold for detection was 0.7 pmol/L. The analysis of PTH has a total CV of 5.9 per centat 7 pmol/L and 5, 9 per cent at 100 pmol/L.

Statistical analysis

Data analysis was performed with STATA v 12.0 (StataCorp LP, Texas, USA). Values are expressed as medians (interquartile range, IQR) and numbers (percentages) unless stated otherwise. Medians (IQR) of PTH and calcium were calculated in groups defined by medication with calcium and/or Vitamin D at different times of follow up. Binary logistic regression analysis, yielding odds ratios (OR) with 95 per cent confidence intervals (CI), was performed using oral calcium or vitamin D analogue medication at last follow up as outcome, with PTH and calcium levels the first day after surgery as independent (predictor) variables. PTH-levels were log-transformed due to skewness, and calcium levels in mmol/l were multiplied with 100, before entered into the multiple logistic regression. The regression analysis also included age as a continuous variable; gender; preoperative PTH and calcium levels, which were transformed in the same way as postoperative values; the number of parathyroid glands identified, divided into three categories: 0-1, 2, 3-5; whether parathyroid auto transplantation was performed or not; and whether the operation was performed due to thyreotoxicosis, benign goitre or due to malignancy. Finally, the rate of permanent hypoparathyroidism was compared in categories of PTH and calcium: for PTH, < 0.7 pmol/l, 0.7-1.6 pmol/l and > 1.6 pmol/l, and for calcium: < 2.00 mmol/l, 2.00-2.15 mmol/l and > 2.15 mmol/l, using two-sided Chi2 and Fishers exact test, where appropriate. A p-value of < 0.05 was considered significant.

Results

Study 1

Some 51 patients (39 women and 12 men) were randomised. Twenty-seven patients were randomised to the HS group and 24 patients to the conventional group (Fig.1). The two groups were well balanced and did not differ in recorded preoperative clinical and biochemical variables (Table 1).

Table 1. Clinical and biochemical preoperative variables

	HS group n=27	Conventional group n=24	P value
Gender male/female	9/18	3/21	0.11
Age (years)	42 (20-70)	34 (20-59)	0.16
P-calcium (mmol/L)	2.42 (2.09 - 2.53)	2.41 (2.25 – 2.67)	0.37

HS; harmonic scalpel

Operating time in the HS group was shorter (median, 121 min; range 84 - 213 min) compared to the conventional group (median, 172 min; range 66 – 268 min); p=0.011). There was no difference in per-operative bleeding between the groups (p=0.42, Table 2). Four patients in the HS group and one in the conventional group experienced transient recurrent nerve palsy (p=0.35). However, no patient developed a permanent paresis of the recurrent laryngeal nerve. One patient in the conventional group was treated by vitamin D analogue therapy at six month follow-up and was considered to suffer from permanent hypoparathyroidism. No other per-operative complications were noted.

Table 2. Recorded intra- and postoperative variables in the two groups of patients

	HS group, n=27	Conventional group, n=24	P value
Operating time (min)	121 (84 – 213)	172 (66 – 268)	0.01
Operative bleeding (ml)	69 (16 – 279)	79 (20 – 290)	0.42
Number of ligatures (n)	1 (0 – 36)	56 (20 – 120)	<0.01
P- calcium day 1 (mmol/L)	2.10 (1.80 – 2.30)	2.04 (1.69 – 2.43)	0.93
Transient RLN pares (n)	4	1	0.35
Permanent RLN pares (n)	0	0	0
Infection (n)	1	0	0.99
Oral calcium at discharge (n)	7	8	0.56
Oral calcium after 6 weeks, (n)	1	3	0.33
Vitamin D at discharge (n), n	1	5	0.09
Vitamin D at 6 weeks (n)	0	1	0.16
Vitamin D at 6 months (n)	0	1	0.47
Total costs (€)	2,040 (1,614 – 3,214)	2,413 (922 – 3,798)	0.16

HS; harmonic scalpel, €; Euro

Comparison of outcomes intra- and postoperatively between the university hospital and the central hospital are shown in Table 3. There were differences in the number of transient recurrent nerve paresis and the number of ligatures in the HS group. There was no difference in the number of complications between the two hospitals.

Table 3. Comparing the university hospital in Lund versus the central hospital in Kristianstad

	University hospital HS group	University hospital Conv. group	Central hospital HS group	Central hospital Conv. group
Operating time (min)	141 (110 – 213)	175 (66 – 268)	103 (84 – 180)	138 (67 – 290)
Bleeding (ml)	87 (16 – 279)	72 (26 – 173)	54 (18 – 206)	148 (2 – 290)
Total costs (€)	2,303 (1,882-3,214)	2,511 (942 – 3,798)	1,824 (1,614 – 2,772)	1,933 (922 – 3,754)
No. of ligatures (n)	24 (0-36)	48 (20 120)	0 (0 -1)	56 (29 – 100)
Transient RLN pares (n)	0	0	4	1
Permanent RLN pares (n)	0	0	0	0
Permanent hypoparathyroidism (n)	0	1	0	0

*HS= harmonic scalpel, Conv= conventional
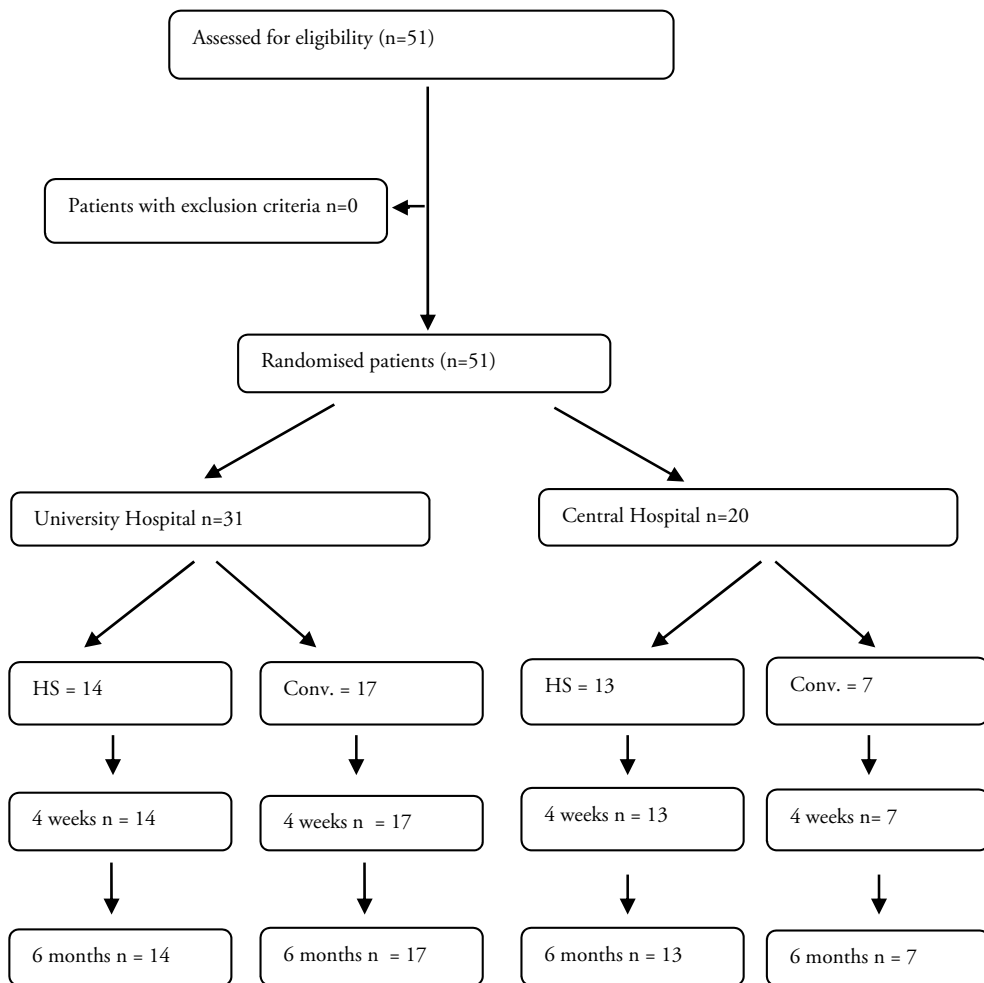
HS= Ultracisison Harmonic Scalpel, Conv.= Conventional technique

Figure 12. Flowchart summerising the prospective controlled trial comparing the use of the Harmonic Scalpel versus conventional haemostatic techniques in patients with Graves´ disease undergoing total thyroidectomy.

Study 2

The cohort consisted of 209 patients, 128 patients with GD and 81 patients with MNG Some 174 patients (83 per cent) were women. Patients with GD were younger than patients with MNG (median age, 35 vs. 51 years; $p<0.001$). Patients with GD also had

a trend towards lower preoperative PTH and serum levels of total calcium, although these differences were not statistical significant, (Table 4).

Table 4. Pre -, peri and postoperative data in patients operated on for Graves' disease and multinodular atoxic goitre

	All patients (n=209) yes/no (%); median (IQR)	Graves´ disease (n=128) yes/no (%); median (IQR)	MNG (n=81) yes/no (%); median (IQR)	P- value
Baseline				
Age (median)	42 (31 – 57)	34 (30 – 48)	55 (40 – 67)	<0.01
Gender male/female	35/174 (17)	26/102 (20)	9/72 (11)	0,08
Preoperatively				
Serum calcium (mmol/l)	2.35 (2.28 – 2.42)	2.34 (2.27 – 2.42)	2.37 (2.29 – 2.43)	0.06
Serum PTH (pmol/l)	3.7 (2.8 – 4.9)	3.5 (2.8 – 4.9)	3.9 (3.1 – 5.0)	0.09
Postoperative in hospital				
Serum calcium (mmol/l) at 18.00 in the evening after operation	2.05 (1.98 – 2-15)	2.04 (1.96 – 2.11)	2.07 (1.99 – 2.19)	0.08
Serum calcium day 1 (mmol/l)	2.00 (1.90 – 2.08)	1.99 (1.88 – 2.06)	2.04 (1.93 – 2.11)	0.81
Serum calcium <2.00, day 1 (mmol/l)	82/127 (39)	51/77 (40)	31/50 (38)	0.82
Serum PTH day 1 (pmol/l)	2.3 (0.8 – 3.9)	2.2 (0.8 – 3.8)	2.5 (0.8 – 3.9)	0.86
Serum PTH <0.7 day 1 (pmol/l)	28/181 (13)	17/111 (13)	11/70 (13)	0.95
Symptoms of hypocalcaemia (n)	71/138 (34)	57/ (44)	14/67 (17)	<0.01
Treatment with i.v. calcium (n)	5/204 (2)	4/124 (3)	1/80 (1)	0.38
Treatment with oral calcium (n)	94/115 (45)	63/65 (49)	31/50 (38)	0.12
Treatment with Vitamin D (n)	33/176 (16)	21/107 (16)	12/69 (15)	0.76
Postoperative at discharge				
Treatment with oral calcium (n)	73/136 (35)	46/82 (36)	27/54 (33)	0.76
Treatment with Vitamin D (n)	33/176 (16)	21/107 (16)	12/69 (15)	0.76
Postoperative follow up at six weeks				
Treatment with oral calcium (n)	31/178 (15)	18/110 (14)	13/68 (16)	0.69
Treatment with Vitamin D (n)	15/194 (7)	7/121 (6)	8/73 (10)	0.23
Serum PTH (pmol/l)	3.8 (2.7 – 4.6)	3.7 (2.8 – 4.5)	3.8 (2.6 – 4.9)	0.89
Postoperative follow up at six months				
Treatment with oral calcium (n)	4/205 (2)	1/127 (1)	3/78 (4)	0.13
Treatment with Vitamin D (n)	2/207 (1)	0/128 (0)	2/79 (2)	0.07

Day 1=first day postoperatively, MNG= multinodular goiter

Three or more parathyroid glands were identified in 61 of the MNG patients (75 per cent) and 109 of the patients with GD (85 per cent), but this difference was not statistically significant. (p=0.08). Almost half of the patients were treated with oral calcium during hospital stay, and 82 patients (39 per cent) had total serum calcium levels lower than 2.00 mmol/l in the morning of the first postoperative day. Five patients received i.v. calcium. At discharge 73 patients (35 per cent) were treated with oral calcium supplements and 33 patients (16 per cent) with vitamin D analogue therapy. Some 28 patients (13 per cent) had a PTH level below the detection limit of the assays on the first postoperative day. At six months, however, only four patients were treated with oral calcium (2 per centand two patients with vitamin D (1 per cent).

The frequency of postoperative biochemical hypocalcaemia did not differ between patients with GD compared with patients with MNG, and postoperative levels of PTH did not differ either. However, symptoms of hypocalcaemia were more common in patients with GD (p=0.001). In multivariable analysis (Table 5), women had a higher risk of postoperative symptomatic and biochemical hypocalcaemia, but had no higher risk of being treated with oral calcium and/or vitamin D at six weeks follow up. Operation due to GD was strongly associated with risk for symptoms of hypocalcaemia, OR 3.26 (1.48 – 7.14), but not with the risk for biochemical hypocalcaemia or treatment with oral calcium and/or vitamin D therapy at six weeks (Table 5). Age showed a borderline inverse association with the risk for postoperative symptoms of hypocalcaemia and for oral calcium treatment at six weeks postoperatively. There was no association between any other factors and the risk for hypocalcaemia.

Table 5. Risk factors for hypocalcaemia in multiple logistic regression model. Odds ratio and 95 per cent confidence interval is shown.

Factor	Symptoms of hypocalcaemia	Biochemical hypocalcaemia	Calcium treatment at six weeks follow up	Vitamin D treatment at six weeks follow up
Age (years)	0.98 (0.95 – 1.00)	1.00 (0.98 – 1.02)	0.96 (0.93 – 1.02)	0.98 (0.93 – 1.02)
Sex				
female	1.00	1.00	1.00	1.00
Male	0.37 (0.15 – 0.93)	0.29 (0.11 – 0.74)	0.26 (0.06 – 1.20)	0.44 (0.05 – 3.75)
Preoperative calcium level (mmol/l)	1.78 (0.10 – 33.48)	0.09 (0.01 – 1.47)	53.41 (1.39 – 2050)	0.58 (0.01 – 238)
Preoperative PTH level (mmol/l)	0.97 (0.79 – 1.19)	1.14 (0.95 – 1.36)	1.03 (0.80 – 1.33)	0.67 (0.40 – 1.12)
Less than 3 identified parathyroidglands				
No	1.00	1.00	1.00	1.00
Yes	1.48 (0.61 – 3.58)	1.32 (0.60 – 2.89)	1.69 (0.51 – 5.61)	0.92 (0.21 – 4.06)
Parathyroid auto-transplantation				
No	1.00	1.00	1.00	1.00
Yes	1.56 (0.72 – 3.40)	0.92 (0.44 – 1.94)	2.30 (0.94 – 5.62)	2.45 (0.71 – 8.41)
Indication for operation				
MNG	1.00	1.00	1.00	1.00
Graves´ disease	3.26 (1.48 . 7.14)	1.02 (0.51 – 2.02)	0.58 (0.22 – 1.53)	0.39 (0.10 – 1.50)

MNG= multinodular goiter

Biochemical hypocalcaemia was defined as total calcium <2.00 mmol/L. Multiple logistic regression analysis with age, preoperative calcium and PTH levels as continuous co- variates, and all others variables as categorical (indicator) co-variates

Study 3

Demographic data and preoperative treatment

A total of 1,157 patients were registered with an operation for GD, 958 women (82.8 per cent) and 199 men. Median age was 35 (range: 7 – 88) years. The preoperative median level of total calcium was 2.36 (IQR: 2.29 – 2.43) mmol/L. Some 424 (36.6per cent) patients were registered with endocrine ophtalmopathy. Eleven hundred and thirty five patients (98.4 per cent) were medically treated before surgery; the most common combination was thyreostatics and thyroxin in 982 patients (86.2 per cent). Beta blockers were used in 192 patients (16.9 per cent) and single therapy in 20 patients (1.8 per cent).

Operation and postoperative hypocalcaemia

The majority of patients were operated with total thyroidectomy. The median operative time (n= 632) was 136 (range: 113 – 164) min. The median weight of the resected specimen (n= 845) was 30 (range: 0 – 48) gram. The median level of total calcium level the first postoperative day was 2.10 (range: 1.97 – 2.22) mmol/L. Seventy four patients (6.4 per cent) were treated with i.v. calcium for symptoms of hypocalcaemia. At discharge, 363 patients (31.4 per cent) were treated with oral calcium at a fixed dose, and 148 patients (12.8 per cent) were treated with vitamin D analogue, both drugs being combined in 124 patients (10.7 per cent).

Follow up

At six weeks follow up 173 patients (15 per cent data missing in 27 patients) were being treated with oral calcium, and 100 patients received treatment with vitamin D (8.6 per cent, data missing in 21 patients). The median level of total calcium was 2.31 (range: 2.23 – 2.38) mmol/L. Unilateral paresis of the recurrent laryngeal nerve was seen in 42 patients and one patient had bilateral nerve paresis. At the six month follow-up, 46 patients (4 per cent, data missing in 35 patients) were being medicated with oral calcium and 45 patients (3.9 per cent, data missing in 22 patients) were medicated with vitamin D, and there were eight patients with paresis of the recurrent laryngeal nerve and one patient had bilateral nerve paresis.

Risk factors for hypocalcaemia

Because not all types of thyroid operations (total thyroidectomy vs. resection) had all possible outcomes, the risk of hypocalcaemia in relation to operation type could not be evaluated by multivariable logistic regression analysis. Instead the risk was evaluated with uni-variable analysis, Table 6.

Table 6. Influence of the type of thyroid surgery on the risk for postoperative medically treated hypocalcaemia in patients undergoing operation for Graves´ disease. Numbers and per cent are shown.

Treatment for hypocalcaemia	Total thyroidectomy, number (%)	Lobectomy and controlateral resection, number (%)	Bilateral subtotal thyroidectomy number (%)	P value *
Intravenous calcium yes/no	66/956 (6.5)	8/75 (9.6)	0/27 (0)	0.22
Vitamin D at discharge yes/no	139/883 (13.6)	6/77 (7.2)	2/25 (7.4)	0.20
Vitamin D at 6 weeks yes/no	91/913 (9.1)	7/73 (8.8)	1/26 (3.7)	0.80
Vitamin D at 6 months yes/no	43/958 (4.3)	2/79 (2.5)	0/27 (0)	0.62

*Fischer´s exact test

Because some data were missing for operative time and weight of the specimen, multivariable analyses were performed with and without the inclusion of these variables. Uni- and multivariable analysis was performed for risk of postoperative medication with i.v. calcium, as well for vitamin D therapy at discharge (table 7), at six weeks (table 8).

Risk factors for treatment with i.v. calcium postoperatively

Young age, low hospital volume of thyroid surgery, long operative time, university hospital versus non-university hospital and operation for re-bleeding were all independently associated with the risk of treatment of hypocalcaemia with i.v. calcium. Not including operative time and weight of specimen in the analysis, the risk factors were young age (OR 0.95; 95 per cent CI 0.91 – 1.00), hospital volume (OR 0.99; 95 per cent CI 0.99 – 1.00), operative time (OR 1.01; 95 per cent CI 1.01 – 1.02), university – vs. non-university hospital (OR 1.32; 95 per cent CI 0.80 – 2.17) and low preoperative levels of total calcium (OR 0.10; 95 per cent CI 0.02 – 0.63) and postoperative infection (OR 6.38; 95 per cent CI 1.49 – 27.40).

Risk factors for treatment with vitamin D analogue at discharge

Operative time, weight of specimen, re-implantation of parathyroid tissue and re-operation for bleeding were all independently associated with treatment with vitamin D at discharge from the hospital. When excluding operative time and weight of the specimen, there was an association between postoperative infection and the risk for treatment with vitamin D at discharge (OR 4.30; 95 per cent CI 1.04 – 17.76), and university versus non-university hospital (OR 2.14; 95 per cent CI 1.21 – 3.67). Preoperative operative treatment with beta blockers showed a borderline association (OR 1.67; 95 per cent CI 0.95 – 2.93) to the risk of treatment with vitamin D table 7.

Table 7. Risk factors for treatment with vitamin D at discharge

Variable	Univariable analysis		Multivariable analysis	
	OR (95 % CI)	P value	OR (95 % CI)	P value
Age, years	0.99 (0.98 – 1.00)	0.10	1.00 (0.97 – 1.03)	0.90
Gender, male/female	0.77 (0.47 – 1.26)	0.30	1.44 (0.56 – 2.05)	0.44
Preoperative total calcium, mmol/L	0.30 (0.07 – 1.23)	0.094	0.36 (0.02 – 3.67)	0.46
Type of hospital, university/other	1.93 (1.32 – 2.84)	0.0008	3.17 (0.87 – 11.59)	0.08
Preoperative Beta blockers yes/no	1.85 (1.23 – 2.80)	0.0032	1.49 (0.57 – 3.91)	0.41
Operative time, min	1.01 (1.00 – 1.01)	0.0001	1.01 (1.00 – 1.02)	0.03
Weight of the specimen,gram	1.00 (1.00 – 1.00)	0.088	1.01 (1.00 – 1.01)	<0.01
Identified parathyroid gland number	1.32 (2.15 – 4.35)	0.0071	0.89 (0.57 – 1.39)	0.60
Auto transplantation of parathyroid tissue yes/no	3.06 (2.15 – 4.35)	<0.0001	5.19 (2.28 – 11.84)	<0.01
Bleeding with re-operation yes/no	2.90 (1.18 – 7.11)	0.020	12.00 (2.43 – 59.28)	<0.01
Postoperative infection yes/no	3.48 (1.03 – 11.69)	0.044	1.45 (0.12 – 14.21)	0.77

*OR= odds ratio.

*Univariable and multivariable logistic regression analysis. This table is redesigned and adjusted, not all variables in the multivariable analysis as in the original paper are listed above

Risk factors for treatment with vitamin D analogue at six weeks

Weight of the specimen and preoperative treatment with beta blockers were associated with an increased risk of treatment with vitamin D at the six week follow-up, whereas re-operation for bleeding showed a borderline association. When excluding operative time and weight of the specimen, this association reached statistical significance (OR 4.01; 95 per cent CI 1.54 – 4-57), table 8.

Table 8. Risk factors for treatment with vitamin D at follow-up six weeks after surgery

Variable	Univariable analysis		Multivariable analysis	
	OR (95 % CI)	P -value	OR (95 % CI)	P- value
Age, years	0.99 (0.97 – 1.00)	0.084	1.00 (0.96 – 1.03)	0.75
Gender, male/female	0.70 (0.38 – 1.28)	0.25	0.89 (0.28 – 2.78)	0.84
Preoperative total calcium, mmol/L	0.26 (0.05 – 1.40)	0.12	0.30 (0.02 – 5.51)	0.42
Type of hospital, university/other	1.14 (0.74 – 1.75)	0.54	2.03 (0.51 – 8.08)	0.31
Preoperative Beta blockers, yes/no	2.39 (1.51 – 3.80)	0.0002	4.20 (1.67 – 10.55)	<0.01
Operative time, min	1.01 (1.00 – 1.01)	0.0040	1.00 (1.00 – 1.01)	0.22
Weight of the specimen, gram	1.00 (1.00 – 1.01)	0.062	1.00 (1.00 – 1.01)	<0.01
Identified parathyroid glands, number.	1.13 (0.90 – 1.42)	0.28	0.86 (054 – 1.37)	0.52
Auto transplantation of parathyroid tissue, yes/no	2.16 (1,43 – 3.26)	0.0003	1.93 (0.78 – 4.78)	0.15
Bleeding with re-operation, yes/no	2.98 (1.08 – 8.20)	0.035	5.01 (0.98 – 25.66)	0.05
Postoperative infection, yes/no	2.09 (0.45 – 9.69)	0.34	2.28 (0.46 – 11.34)	0.32

*Univariable and multivariable logistic regression. This table is redesigned and adjusted, not all variables in the multivariable analysis as in the original paper are listed above

Risk factors for treatment with vitamin D at six months

Re-operation for bleeding and weight of the specimen were independently associated with risk of treatment with vitamin D at six months. However, when operative time and weight of the specimen were excluded from the analysis, re-operation for bleeding was the only independently factor associated with the risk for treatment with vitamin D at this time point (OR 5.47; 95 per cent CI 1.10 – 27.06).

Study 4

Some 519 patients were included, 114 (22 per cent) men and 405 (78 per cent) women, with a median age of 46 (IQR, 32 – 61) years. Three or more parathyroid glands were identified in 371/519 (71.3 per cent) of the patients, and parathyroid auto transplantation was performed in 90/519 (17.3 per cent), Table 9. Permanent hypoparathyroidism, was seen in 10/519 (1.9 per cent) patients. The median (range) follow up in these patients was 2.7 (1.2 – 10.3) years. There was a gradual decrease in

the proportion of patients treated with calcium and/or vitamin D at the later follow ups, Fig 13.
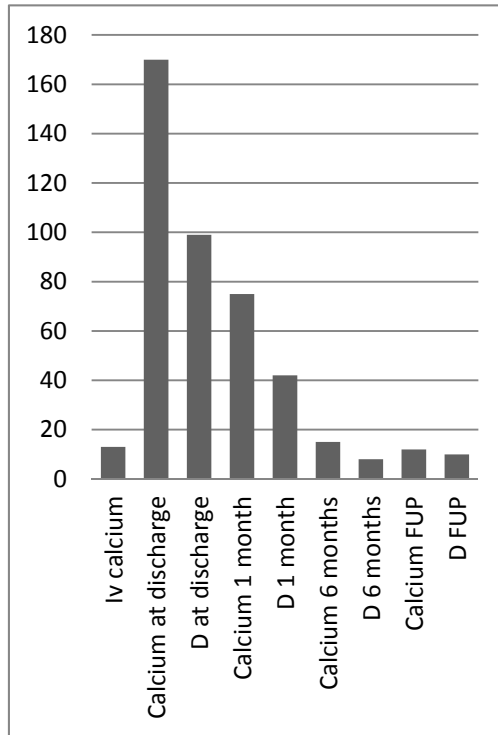
*D= Vitamin D, FUP= last follow-up

Figure 13. Number of patients with oral calcium and/or treatment with Vitamin D at different time points of follow up

Parathyroid hormone (PTH) and calcium levels on postoperative day one were significantly associated with risk of long – term hypoparathyroidism. No patient with auto transplantation of parathyroid tissue developed permanent hypoparathyroidism. Age, gender, indication for surgery, preoperative PTH and calcium levels, and number of parathyroid glands identified, were not associated with permanent hypoparathyroidism in this study (Table 10).

Table 10. Risk factors for treatment with vitamin D at different time points of postoperative follow-up. Logistic regression analysis.Odds ratio (OR) with 95 per cent confidence intervals in single and multiple adjusted models.

Factor		Discharge		1 month		6 months		> 1year	
		OR (95% CI)	OR* (95% CI)	OR (95% CI)	OR* (95% CI)	OR (95% CI)	OR* (95% CI)	OR (95% CI)	OR*(95% CI)
Age		1.00 (0.99-1.01)	1.00 (0.98-1.02)	1.00 (0.98-1.02)	0.99 (0.96-1.01)	1.00 (0.96-1.04)	0.99 (0.94-1.04)	1.00 (0.96-1.03)	0.98 (0.93-1.02)
Gender	Male	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Female	0.75 (0.43-1.31)	1.79 (0.71-4.54)	0.69 (0.30-1.60)	0.55 (0.18-1.66)	0.50 (0.06-4.13)	0.48 (0.05-4.89)	0.89 (0.19-4.23)	0.98 (0.15-6.47)
Preoperative diagnosis	Benign	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Thyreot oxicosis	0.99 (0.54-1.83)	1.28 (0.54-3.04)	0.68 (0.32-1.44)	0.74 (0.25-2.17)	0.49 (0.30-9.16)	0.47 (0.04-5.22)	0.55 (0.12-2.51)	0.30 (0.03-2.88)
	Cancer	0.87 (0.53-1.42)	0.81 (0.31-2.11)	1.83 (0.74-3.59)	1.77 (0.63-4.97)	1.81 (0.08-2.89)	1.82 (0.27-12.3)	1.35 (0.30-6.17)	0.99 (0.15-6.57)
Preoperative serum calcium (mmol/L[a]		0.99 (0.97-1.01)	0.99 (0.96-1.02)	0.98 (0.95-1.01)	0.99 (0.95-1.03)	0.96 (0.90-1.04)	0.99 (0.90-1.08)	0.96 (0.90-1.03)	1.01 (0.94-1.09)
Preoperative serum PTH (pmol/l)[b]		1.02 (0.58-1.79)	1.43 (0.60-3.37)	0.54 (0.23-1.25)	0.54 (0.18-1.60)	0.78 (0.14-4.49)	0.71 (0.08-6.72)	0.59 (0.12-2.86)	0.47 (0.05-4.36)
Number of identified parathyroid glands	0-1	1.07 (0.62-1.86)	1.52 (0.64-3.61)	1.76 (0.77-3.99)	1.95 (0.69-5.53)	1.79 (0.39-8.11)	1.60 (0.26-9.71)	2.25 (0.53-9.57)	1.81 (0.31-10.65)
	2	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	3-5	1.19 (0.71-2.00)	1.08 (0.50-2.74)	1.81 (0.82-3.98)	1.48 (0.55-3.97)	0.37 (0.04-3.59)	0.31 (0.03-3.72)	0.74 (0.12-4.50)	0.74 (0.09-6.43)
Parathyroid auto-transplantation	Yes	1.00	1.00	1.00	1.00	1.00	1.00	No events.	
	No	0.41 (0.25-0.68)	0.49 (0.23-1.06)	0.43 (0.21-0.86)	0.53 (0.22-1.31)	1.48 (0.18-12.15)	1.40 (0.13-15.24)		
Serum calcium day one (mmol/l)[a]		0.91 (0.89-0.93)	0.94 (0.92-0.97)	0.94 (0.91-0.96)	0.97 (0.94-0.99)	0.91 (0.87-0.96)	0.94 (0.89-0.99)	0.92 (0.88-0.96)	0.95 (0.90-0.99)
Serum PTH day one (pmol/l)[b]		0.06 (0.04-0.11)	0.10 (0.06-0.19)	0.27 (0.19-0.38)	0.29 (0.19-0.43)	0.34 (0.20-0.97)	0.45 (0.22-0.89)	0.28 (0.17-0.45)	0.32 (0.17-0.60)

*Adjusted for all factors in table. a) Calcium level*100 b) log PTH
OR; odds ratio, CI; 95 per cent confidence interval

Discussion

Thyroidectomy is the most frequently performed operation in endocrine surgery. Complications to thyroid surgery are rare but can be life-threatening as for postoperative bleeding with airway compression and bilateral palsy of recurrent laryngeal nerve (RLN). Other complications, such as permanent hypoparathyroidism and unilateral palsy of RLN are associated with chronic medication or disability. Since many patients who undergo thyroid surgery are young and at working age, postoperative complications are not only important for the individual but also have a great socioeconomic impact. Overall, the rate of complications in the present studies were low: temporary RLN paresis ranged from nil (paper I) to 3.6 per cent (paper III), and permanent RLN paresis was 0.5 per cent (paper III). However transient postoperative hypocalcaemia was not uncommon. The rate of transient hypocalcaemia was 39 per cent in paper II and 31.4 per cent in paper III. Permanent hypocalcaemia was 3 per cent in paper II and 4 per cent in paper III.

Operation technique and adjuncts (paper I)

The main purpose of paper I was to compare two different operation techniques in total thyroidectomy in patients with GD. The primary endpoint was operation time and secondary endpoints were rates of complications and costs. The operation time was shorter in patients operated with Harmonic scalpel® compared to conventional techniques (knot tying, clips, and diathermy) and permanent complications did not differ between the two groups. Since operation time was shorter in the Harmonic scalpel group, total costs were lower in this group. The results in paper I are broadly in agreement with other studies within the field [81]. The introduction of new vessel sealing devices in general surgery during the last decades, such as Harmonic scalpel®, Ligasure™ and Biclamp®, has been shown to shorten operation time without increasing complications. The same development has been seen in thyroid surgery [36, 82-84].

One of the most important side effects of the new vessel sealing devices is lateral thermal spread to the surrounding tissue. Sutton et al [38] reported that the degree of lateral thermal spread varies with power settings and application time. In Suttons in vitro study, the mean temperature at the tip of the Harmonic scalpel instrument after 5 sec application and at the highest power setting was 48 °C compared to 42 °C with bipolar

diathermy and 79 °C with monopolar diathermy. Koch et al [85] performed an experimental *in vitro* and *in vivo* animal study with tissue from lung parenchyma, tongue and parotid gland. These authors suggested a safety margin of at least 3mm to be justified as a conservative limit between the site of energy application and the organ at risk. In paper I, albeit not statistical significant, a larger number of transient paresis of the RLN was found in the Harmonic scalpel® group. However, there was no patient with permanent nerve paresis in the Harmonic scalpel® group. The reason for this finding may be that the recommended safety margins were not followed. In agreement with the results in the present study, a meta-analysis of vessel sealing devices in thyroid surgery [86], found that the use of Harmonic scalpel® was associated with fewer patients with postoperative hypoparathyroidism but a higher frequency of paresis of the RLN compared to conventional techniques and Ligasure™.

Hypocalcaemia and hypoparathyroidism (papers II-IV)

Definition of hypocalcaemia and hypoparathyroidism

Hypocalcaemia is not always associated with accompanying symptoms. The traditional methods for detecting hypocalcaemia in the postoperative period include close clinical monitoring of symptoms of hypocalcaemia and measurements of total or ionized calcium levels.

Hypoparathyroidism is by definition an inadequate secretion of PTH in response to low serum calcium levels. In the present studies hypocalcaemia was defined as a level of total calcium of less than 2.00 mmol/L and simultaneous symptoms of hypocalcaemia. This definition is quite common in the literature [59, 87].

However, some authors have defined hypocalcaemia as a serum level of total calcium below1.75 mmol/L and some as a level of total calcium below 2.15 mmol/L, e.g. below the normal range [88, 89]. The different definitions of hypocalcaemia make it difficult to compare outcomes between different studies. Mehanna et al highlights this problem in a review article; the range of postoperative hypocalcaemia varied between 0 – 46 per cent depending on definition. [90]. Further, there is no consensus if postoperative calcium levels should be measured as serum total calcium or ionized calcium. Some reports even include patients undergoing hemithyroidectomy, where the risk for hypocalcaemia is virtually nil. An international accepted definition of transient - and permanent hypocalcaemia is clearly highly warranted. Mehanna et al proposed the following; "postoperative hypocalcaemia is an adjusted serum calcium level at any point after the operation below the institutions reference range, requiring treatment with vitamin D derivatives and/or calcium supplements, to correct falling serum calcium within institutional reference range and/or treatment". For permanent hypocalcaemia

Mehanna et al suggest: " any patient included in above definition of postoperative hypocalcaemia, who still requires treatment six months or longer after date of surgery" [90].

Overall rate of hypocalcemia

Permanent hypocalcaemia has become the most common complication after thyroid surgery. The overall incidence of postoperative hypocalcaemia following total thyroidectomy is between nil and 46 per cent depending on definitions [91, 92].

If permanent hypocalcaemia is defined as continuous treatment with calcium and or vitamin D after six months the prevalence in the literature is between 2.7 and 6 per cent [93, 94]. In paper III, the frequency of permanent hypocalcaemia, with the definition above was four per cent. However, in paper IV, the overall rate of permanent hypoparathyroidism was 1.9 per cent which is in line with previous reports from high volume centers [49, 95].

Risk factors for hypoparatyroidism

Age

Both young age [61, 92] and old age [59, 96, 97] has been suggested as a risk factors for postoperative hypocalcaemia. In paper II we found that younger patients experienced more symptoms of hypocalcaemia. The reasons for the diverging results remain obscure. Better et al induced acute hypocalcaemia in young subjects (mean age 32.3 years) and elderly subjects (mean age 71.0 years), by infusion of neutral phosphate. No difference was observed in the ability of the two groups to restore the normal serum calcium level at 24 hours after infusion. In the same study, there was a difference between the two groups regarding phosphaturic response, with an increased excretion of urinary phosphate in the elderly age group compared to the younger group [98]. The reason why younger patients may develop more symptoms of hypocalcaemia after thyroidectomy remains unexplained but it may be hypothesized that nerve conduction in younger patients are more sensitive to alterations in the calcium metabolism compared with older patients [99, 100]. Ionized fraction of calcium remains stable throughout life but total calcium usually decrease with older age, probably related to decrease in albumin concentration. In the present studies total serum calcium was used to define biochemical hypocalcaemia and one may argue that ionized calcium is a more stable marker of postoperative hypocalcaemia[25].

Gender

Several studies have found female gender to be associated with higher risk of postoperative hypocalcaemia [50, 101, 102]. The reason for this discrepancy in postoperative hypocalcaemia between men and females is unknown and the present studies could not support these earlier findings.

Type of thyroid disease

In paper II the risk of postoperative symptomatic and biochemical hypocalcaemia were compared in two groups of patients undergoing total thyroidectomy: patients with GD and patients with MNG. Younger patients, specifically with GD, experienced more symptoms of hypocalcaemia compared to patients with MNG. There were, however, no biochemical differences between the two groups of patients pre- and postoperatively. Previous studies have suggested that patients with GD are at increased risk of hypocalcaemia postoperatively compared to operation for other benign thyroid diseases, because of increased technical demands at surgery due to inflammation [50, 59, 92, 103]. It is well recognized by most surgeons, that operation for GD is more technically demanding than operations for MNG. In GD there are often more adhesions between the thyroid and the parathyroid glands compared to other benign thyroid disease. The situation with more adhesions may cause diffuse bleedings and reduced visibility during the operation and perhaps increases the risk of injure to the circulation to the parathyroid glands.

Identification of the parathyroid glands

Identifying all four parathyroid glands during operation is recommended by many authors as a way to decrease the risk of postoperative hypocalcaemia. However, this approach has recently been questioned. A systematic review of retrospective studies, including 1068 patients, showed that identification of three to four parathyroid glands peroperatively, was associated with a higher risk of incidental parathyroidectomy compared to the identification of nil to two parathyroid glands [104]. A study with 3,660 patients undergoing thyroid surgery showed that lower numbers of identified parathyroid glands peroperatively were associated with higher risk of postoperative hypocalcaemia [67]. More recently, in a meta-analysis of 115 publications, identifications of fewer than two parathyroid glands at operation were associated with permanent hypocalcaemia [105]. In the present papers II, III and IV, the numbers of identified parathyroid glands were not associated with increased risk of postoperative

hypocalcaemia, and the number of identified parathyroid glands could not predict a permanent hypocalcaemia.

Accidental removal of the parathyroid glands

The frequency of accidental removal of parathyroid glands in the literature is reported to be 5 to 20 per cent and in 40 to 50 per cent of these patients , the excised parathyroid gland is located within the thyroid gland, making peroperative identification impossible [106]. In studies II-IV it is not know if parathyroid glands were accidentally removed or not.

Autotransplantation

Auto transplantation of parathyroid tissue has been suggested to decrease the risk of permanent hypocalcaemia [48, 107-109]. However, some studies show that auto transplantation may increase the risk of transient postoperative hypocalcaemia.[109, 110]. In paper II, auto transplantation of parathyroid glands were not associated with increased risk of either transient or permanent hypocalcaemia. However, in paper III auto transplantation of the parathyroid glands was a risk factor for transient postoperative hypocalcaemia, defined as treatment with calcium and or vitamin D at discharge, but not with permanent hypocalcaemia. The difference between these two results may depend upon the smaller number of patients included in paper II, or that paper III only included patients with GD. A meta-analysis of four studies including 823 patients, showed a significantly higher risk of transient hypocalcaemia in patients who had one or more parathyroid gland auto transplanted [105]. Judging the viability of the parathyroid glands to predict postoperative insufficiency of the gland in situ is very difficult. Khuhel et al [111] found that the absence of discoloration is not reliably to determine whether the parathyroid blood supply is in intact. It is therefore recommended to leave as many parathyroid glands in situ as possible. Similar results were reported in a study by Ohman et al in 1978, where an increased risk of permanent hypocalcaemia in patients with auto transplanted parathyroid glands were noted. The authors suggested that all efforts should be made to leave the parathyroid glands in situ [112]. In agreement, Pattou et al [113] showed that half of the patients who developed permanent hypoparathyroidism had one or two parathyroid gland auto transplanted. Sitges-Serra reported a 5 per cent rate of permanent hypocalcaemia after auto transplantation and 2.4 per cent when all four parathyroid glands were left in situ [48]. However, according to a recent meta-analysis of Edafe et al there was no association between parathyroid auto transplantation and permanent hypocalcaemia[105]. In the present paper IV there were no patients with permanent hypoparathyroidism after intraoperative auto transplantation of parathyroid tissue. Therefore, the results suggest that parathyroid auto transplantation seem to be warranted as a way to minimize the risk of permanent hypocalcaemia, but this issue will be a matter of debate. Again, one

may speculate if some of the conflicting results concerning auto transplantation of the parathyroid glands and the risk of hypocalcaemia derives from the problems discussed above concerning the definition of hypocalcaemia and hypoparathyroidism..

Preoperative medical treatment

The patients in the current studies were euthyroid prior to surgery. In patients with GD a combination of thyroxin and thyreostatics was used in 86 per cent of the patients and additionally almost 17 per cent were treated with beta-blockers. Beta-blockers ameliorate the symptoms of hyperthyroidism that are caused by increased beta-adrenergic tone. These include palpitations, tachycardia, tremulousness, anxiety and heat intolerance. Nonselective beta-blockers, such as propranolol, are preferred because they have a more direct effect on hyper metabolism and it´s inhibitory effects may be due to a membrane stabilizing effect rather than to genuine beta adrenoceptor blockade [114, 115]. Interestingly, patients with GD that were treated preoperatively with beta-blockers had a higher risk for being treated with vitamin D at follow up after six weeks (paper III). There was also a borderline association between preoperative uses of beta – blockers and treatment of vitamin D at discharge. Studies have shown that injection of epinephrine causes a significant prompt increase in serum PTH level, without increase in serum level of calcium. Further studies have shown that propranolol infusion alone significantly inhibits the basal secretion of PTH and this was overcome by epinephrine administration [116, 117]. The reason for the association between beta-blockers and hypocalcaemia in patients with GD found in paper III is not clear, but it may be suggested that patient treated with beta-blockers suffer from a more severe hyperthyroidism with symptoms masked by medications. Other medications preoperatively were not associated with postoperative hypocalcaemia such as antithyroid drugs, lugol´s solutions or cortisone, which is in agreement with other studies[105].

Extent of surgery

Multinodular goiter (MNG) is one of the most prevalent thyroid disorders worldwide. In recent years total thyroidectomy has been more accepted as the treatment of choice for MNG if the patient has bilateral thyroid disease [44, 118, 119]. The vast majority of the thyroid procedures reported in this thesis was total thyroidectomies. In paper III some patients with subtotal or near total thyroidectomies were included but the numbers were so small that the extent of surgery could not be included within the multivariable analysis. In paper III, operation time and weight of the specimen,

regarded as proxies for the extent of dissection, were found to be risk factors for medically treated postoperative hypocalcaemia. Other studies which analysed risk factors for postoperative hypocalcaemia reported that the extent of surgery is one of the major risk factor for both transient and permanent hypocalcaemia in thyroid surgery [50]. In agreement, in a retrospective study of 2000 thyroid procedures, Karamanakos et al [120] reported a significant correlation between the extent of surgery, and transient and permanent postoperative hypoparathyroidism.

The only substantial argument against total thyroidectomy is its potentially higher associated complication rate compared to subtotal thyroidectomy. However, with appropriate surgical technique, complications can be minimized and the recurrence of disease is eliminated[43, 119].

Surgeon and institution operation volume

A recent study [121] which analyzed the impact of the extent of surgery in patients with GD, confirmed the safety of total thyroidectomy for benign thyroid disease in high volume centers. In recent guidelines from the American Thyroid Association and the American Association of Clinical Endocrinologists, it is recommend to refer patients with GD for total thyroidectomy or near total thyroidectomy to high volume thyroid surgeons to keep the risk of permanent morbidity as low as possible[122].

Sosa et al[123] showed that surgeons performing more than 100 thyroid procedures per year had a significantly lower complication rate compared to surgeons performing less than 100 operations under same time period. Similar results was reported by Gourin et al, who showed that the proportion of thyroid procedures performed by high volumes surgeons and in high volume centers have increased during the last decades[46]. Breuer et al suggested that excellent and equivalent outcomes can be achieved for surgery for GD in children and adults when treated at high volume centers[124].

There was no data on individual surgeon volume in the present studies but in papers I and II, all surgeons performed at least 50 thyroid operations annually. For the same reason, surgeon´s volume could not be used in the analyses of risk factors for postoperative hypocalcaemia.

Prediction of transient and permanent hypoparathyroidism

Many studies have reported that postoperative calcium measurement on day 1 is of value to predict transient hypocalcaemia [110, 125, 126]. In paper III, an inverse association between low preoperative calcium levels and the risk for postoperative treatment with iv. calcium treatment was found, and this is in agreement with previous studies [61]. Furthermore, low calcium levels (< 2.00 mmol/L) at one to three weeks after surgery has been associated with permanent hypocalcaemia [113].

PTH measurements intraoperatively is by many authors considered as a useful tool to identify patients at high risk for postoperative hypocalcaemia [127-129]. A low postoperative PTH level is associated with postoperative hypocalcaemia by most authors, and a decline of PTH by more than 37.9 – to 88 per cent compared to preoperative levels had a high sensitivity (70 to 100 per cent) to predict transient hypocalcaemia[27, 52, 130-132]. The timing of intraoperative- or postoperative PTH measurement for predicting postoperative hypocalcaemia has been controversial. In a prospective study, Kim et al reported on 108 patients, and measured PTH at 0 hr, 6 hr, 12 hr, 24 hr, 48 hr and 72 hr postoperatively. These authors found that the PTH levels predicted hypocalcaemia at all-time points, except at 0 hr [56]. In a systematic review by Edafe et al, there was only one study where PTH level below 6 pg/ml (<0.7 pmol/L) or less at 3 hr postoperatively had a high sensitivity for predicting permanent hypocalcaemia [133]. However, a low PTH concentration predicts patients at risk of hypocalcaemia during the first 24 hours and a normal level excludes permanent hypocalcaemia[105].

In paper IV, low PTH levels measured early postoperatively, at the end of operation or at postoperative day one, were strongly associated with risk of permanent hypocalcaemia. The rate of permanent hypocalcaemia in our study was 19 per cent in patients not auto transplanted and with undetectable PTH the day after surgery.

Methodological considerations (paper I-IV)

A strength of the first study (paper I) is the homogeneity of the patient cohort – only patients undergoing total thyroidcetomy for GD were included. The randomized design and the fact that that operations were performed in an academic teaching institution as well as in a county hospital, is an advantage. Despite a small number of patients, the study was adequately powered to detect differences in the main outcome.

In paper II the aim was to compare the risk for postoperative symptomatic and biochemical hypocalcaemia at different time points of follow up in patients undergoing total thyroidectomy for GD versus patients with MNG. The strengths of the study

included a homogenous dataset of patients and that all patients were operated on by the same surgical team in the same hospital. Limitations in this paper were relatively small number of patients, missing data of potentially important factors for postoperative hypocalcaemia such as operation time, weight of the specimen, and information on vitamin D levels and medication of importance for calcium metabolism. There were no differences between the two groups in clinical and biochemical pre, intra and postoperative variables, apart from symptoms of postoperative hypocalcaemia which were more common in patients with GD. With larger number of patients, differences between the two groups for instance in postoperative calcium and PTH levels might have been more apparent but probably still clinically small.

In paper III the data was extracted from the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal Surgery (SQRTPA) (http://www.thyroid-parathyroidsurgery.com). Strengths of the study included the prospective data collection and a high participation rate of centers in Sweden. The coverage of the clinics responsible for thyroid surgery in this data base is approximately 95 per cent(2012) and these clinics perform 98 per cent of all the thyroid procedures in Sweden [134], which makes external validity high. A further strength of the study was that several potentially important variables could be included in the multivariable analysis; apart from age and gender, operative time preoperative medical treatment and complications. Limitations in paper III are, for example, missing values for operation time and the weight of the specimen, and individual surgical experience, all known or suspected factors of importance for complications. However, for variables with a larger number of missing values, data were analysed with multiple variable logistic regression with and without these variables. The results were practically identical, suggesting that the obtained results are robust. During the study period, different departments joined the SQRTPA at different time points. Therefore, the impact of hospital volume of thyroid surgery on outcome was evaluated by data from the Swedish National Board for Health and Social Welfare as a proxy. Another limitation in paper III is that pre- and postoperative PTH levels and the levels of vitamin D levels are not registered in SQRTPA. In paper III, hypocalcaemia was pragmatically defined as patients being treated with calcium and/or vitamin D at different time points.

In paper IV, the advantages of the study are the homogenous dataset and that patients were operated by the same surgical team, in the same hospital, with similar surgical technique. Outcome measures were meticulously recorded, and all patients taking oral calcium and/or vitamin D at six months were followed for at least one year. Several limitations are noted; information on all risk factors for hypoparathyroidism was not collected in all patients. Missing values occurred for some of the variables: operation time, weight of the specimen and whether lymph node dissection was performed or not. A total number of 66 (12.7 per cent) patients had missing information regarding the PTH level on day one after surgery. If values on PTH levels on postoperative day

one were missing, they were replaced by the PTH value immediately after surgery since there was good correlation between these levels. This is also in agreement with the findings in the recent review and meta-analysis by Edafe et al[105].

Table 11. A summary of strengths and weakness paper I-IV

Paper	Strengths	Limitations
I	Homogenous cohort of patients (Graves ´disease), the same operation procedure (total thyroidectomy), a consecutive group of patients, operation performed at two clinics; a university clinic and a non-university clinic.	Small numbers of patients, pragmatic definition and treatment of postoperative hypocalcaemia
II	Homogenous dataset, same surgical team in one hospital	Small numbers of patients, lack of some data such as operation time, weight of the specimen, co-morbidities of the patient
III	Large study in a homogenous cohort of patients, prospective data collection. Inclusion of several potential important variables in the multivariable regression analysis	Lack of information on individual surgical experience and volume. Some missing values that could affect long term outcome. Lack of data for PTH levels, vitamin D levels, magnesium levels
IV	Homogenous dataset, patients were operated by the same surgical team, in the same hospital.	All risk factors for hypoparathyroidism were not captured in all patients, e.g., operation time and weight of the specimen. Lack of information if lymph node dissection was performed or not

Conclusions

- In patients undergoing total thyroidectomy due to Graves' disease, surgery performed by the use of Harmonic Scalpel decreased operation time compared with conventional techniques without increasing complications or costs.

- Patients with Graves´ disease were younger and experienced more often symptoms of hypocalcaemia after total thyroidectomy compared with patients operated due to multinodular goitre. There were no differences in PTH or calcium levels between the two groups of patients' pre-or postoperatively, and no differences in supplementation of oral calcium or vitamin D at discharge or at follow up.

- Risk factors for medically treated hypocalcaemia after total thyroidectomy in patients with Graves´ disease are multifactorial and vary over follow-up time. Patients with large goitres and patients that were re-operated due to postoperative hematoma had a higher risk of postoperative hypocalcaemia. Patients who were treated with beta blockers prior to operation had a higher risk of medically treated hypocalcaemia in the early follow up period.

- A low PTH level early after total thyroidectomy was associated with a high risk of permanent hypoparathyroidism. Normal levels of PTH exclude long-term hypoparathyroidism. There is no clear cut-off to indicate high or low risk for permanent hypoparathyroidism by calcium, and the levels of calcium postoperatively cannot be used to accurately predict long-term risk for this complication. Parathyroid auto transplantation seems to be warranted as a way of minimizing the risk of permanent hypoparathyroidism.

Future aspects

Total thyroidectomy has become the treatment of choice by many surgeons for benign thyroid disease, and complications are in general uncommon. Even though there are differences in complication rates between different types of thyroid operation such as transient RLN paresis and postoperative hypocalcaemia, the beneficial outcome of TT with no risk for recurrent disease, makes the TT an attractive surgical alternative. To reduce complication rates in thyroid surgery is a challenging task as the complication rate is low. However, operations performed in high volume centres has been shown to reduce complications further[123, 135]. A definition of postoperative hypocalcaemia varies between studies which hampers interpretations of results. It is therefore very important to have clear and accepted international definitions of postoperative hypocalcaemia. Ionized calcium is preferred for evaluating postoperative hypocalcaemia, as it is quite stable over years whereas total calcium tends to decrease with older age.

Nerve monitoring is a new and promising instrument in thyroid surgery and is in use in many clinics performing thyroid surgery. Even though there are still no data showing that nerve monitoring decreases the rate of permanent RLN paresis, it´s use is considered beneficial in more extended thyroid surgery and in patients undergoing reoperation. Some authors' suggest that continuous nerve monitoring of the vagal nerve gives better information on possible injury of the RLN. Probably more studies on nerve monitoring will be published in the future; the area remains controversial.

Thyroid surgery has been performed with a standard Kocher incision on the neck over the thyroid isthmus for more than 100 years. In recent years, various new techniques of minimally invasive thyroidectomy have emerged. These include approaches to the thyroid from the neck, the axilla, the breast, the retro-auricular space, and even the mouth. Robotic surgery was introduced to the head and neck area in 2005. This "minimal invasive technique" allows the surgeon to operate through a smaller incision than would otherwise be required during traditional open surgery. The benefits of minimally invasive surgery are perhaps small incisions and less pain[136, 137]. To our knowledge, no patient has been operated by robotic thyroidectomy in Sweden. Which approach that will be the preferred in the future is difficult to predict; minimal invasive and robotic thyroidectomy are still at an experimental stage in many countries. The operation time is often longer and the new surgical approaches and techniques are more expensive. Open surgery today is performed with short operation time, minor discomforts, low complication rates and short hospital stay. It is therefore highly

unlikely that minimal invasive or robotic thyroidectomy will become standard approaches for patients in most hospitals.

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Populärvetenskaplig sammanfattning

Sjukdomar i sköldkörteln (thyroidea) finns dokumenterade i litteraturen sedan nästan 3000 år tillbaka. Många miljoner människor över hela världen lider av någon typ av sköldkörtelsjukdom. En förstorad sköldkörtel benämns som struma, men säger inget om den bakomliggande orsaken. En förstorad sköldkörtel kan vara elakartad (cancer) eller godartad, vanligtvis så kallad knölstruma. Patienten kan ha normal eller ökad ämnesomsättning. Ett exempel på den senare är Graves' sjukdom, en autoimmun sjukdom som förutom ökad ämnesomsättning även kan ge ögonsymptom. Vissa sjukdomar behandlas med läkemedel medan andra behandlas mest effektivt med kirurgiskt ingrepp. Sköldkörteln producerar hormoner för kroppens ämnesomsättning, tyroxin (T4) och trijodidtrionin (T3). Dessa hormoner reglerar hur kroppen utvinner energi ur födan. Om sköldkörteln inte fungerar normalt, med för låg eller hög hormonnivå använder kroppen energin långsammare eller snabbare än normalt. Total thyroidektomi (borttagande av hela sköldkörteln) vid Graves´ sjukdom, uppfattas av många kirurger som en av de svårare av ingreppen på sköldkörteln med en ökad risk för komplikationer, såsom skada på stämbandsnerven, blödning och sänkt kalcium (hypokalcemi). Graves´ sjukdom kan behandlas med läkemedel (thyreostatika) och radiojod, men risken är att patienten drabbas av återfall i sjukdomen. Vid svårare fall av Graves´ sjukdom, behandlas patienten även med så kallade betablockerare, en medicin som bland annat minskar symptom på ökad ämnesomsättning som hjärtklappning darrhänthet och svettningar. Svåra ögonsymptom behandlas med kortison och i vissa fall med operation., Principen för radiojodbehandling är att utnyttja sköldkörtelns förmåga att ta upp och lagra jod. Thyreostatika minskar produktionen av sköldkörtelhormonerna tyroxin, T4, och trijodtyronin, T3, i sköldkörteln. Höga doser av läkemedlet kan helt stoppa produktionen av sköldkörtelhormon. Radioaktiv form av jod (I-131) ansamlas i körtelvävnaden och avger strålning med mycket kort räckvidd och destruerar körtelvävnaden. Sköldkörteln är ett synnerligen kärlrikt organ och därför är det viktigt med noggrann blodstillning under operationen. Med noggrann blodstillning blir det också lättare att identifiera stämbandsnerverna och bisköldkörtlar, vars hormon, bisköldkörtelhormon (PTH), styr kalciumomsättningen i kroppen. Komplikationer till sköldkörtelkirurgi är generellt relativt sällsynta men kan vara livshotande, som t.ex. blödning efter operation med akuta andningsproblem. Andra komplikationer kan leda till kronisk medicinering (lågt blodkalcium) eller invaliditet (skada på stämbandsnerven). Lågt blodkalcium efter sköldkörteloperation, hypokacalcemi, är den vanligaste komplikationen till total thyroidektomi. Hypokalcemi kan ge symtom bl.a. i form av stickningar i fingrar och runt munnen men

i mer avancerade former kan det leda till muskelkramper. Skada på stämbandsnerven ger symptom i form av heshet och i värsta fall, andningsproblem. Det är därför viktigt att identifiera faktorer som ger en ökad risk för komplikationer vid thyroidea kirurgi.,

I den första studien i denna avhandling jämfördes två olika operationstekniker vid sköldkörteloperation hos patienter med Graves' sjukdom. I den ena gruppen användes konventionell operationsteknik med ligatur och diatermi för att uppnå blodstillning, och i den andra gruppen användes ultraljudskniv (Harmonic Scalpel®), ett instrument som delar och stänger kärl med ultraljudsvibration. Resultaten visade på en kortare operationstid i gruppen som opererades med ultraljudskniv utan ökad risk för komplikationer.

Många kirurger anser att risken för komplikationer vid sköldkörteloperation hos patienter med Graves' sjukdom är högre jämfört med operation för andra sköldkörtelsjukdomar. I den andra studien i avhandlingen jämförde vi två olika patientgrupper, en grupp med godartad knölstruma med normal ämnesomsättning och en grupp patienter med Graves´ sjukdom. Samtliga patienter blev opererade med borttagande av hela sköldkörteln. Resultaten visade inte någon skillnad irisk för komplikationer mellan grupperna. Yngre patienter, som framförallt utgjordes av patienter med Graves´ sjukdom, upplevde dock mer symtom av hypokalcemi. Trots detta skilde sig inte nivån av blodkalk eller bisköldkörtelhormon åt mellan de två grupperna och inte heller andelen patienter som behandlades med D-vitamin eller kalcium efter operation. Resultatet kan möjligen förklaras av att samtliga patienter var välbehandlade med normal ämnesomsättning innan operationen, vilket sannolikt minskar risken för lågt blodkalk efter ingreppet.

I den tredje studien analyserade vi riskfaktorer hos patienter med Graves´ sjukdom för symptomgivande hypokalcemi efter sköldkörteloperationen. Hypokalcemi definierades som lågt blodkalk som krävde medicinsk behandling med kalcium och/eller D-vitamin. Patientdata var registrerad i det skandinaviska kvalitetsregistret för thyroidea, parathyroidea och binjure kirurgi. Resultatet visade att patienter med Graves´ sjukdom som förbehandlas med beta blockad inför kirurgi, hade en ökad risk för behandlingskrävande hypokalcemi vid första uppföljningen efter ca sex veckor. Reoperation för postoperativ blödning och samt större vikt på den avlägsnade sköldkörteln var riskfaktorer för behandling med vitamin D vid sex månaders uppföljning av patienterna.

I det fjärde arbetet undersöktes riskfaktorer för permanent hypokalcemi hos patienter som opererats för sköldkörtelsjukdom vid kirurgiska kliniken vid Skånes Universitetssjukhus i Lund. Analysen visade att lågt eller omätbart PTH tidigt efter operation innebar en ökad risk för långdragen eller permanent hypokalcemi. Vidare var transplantation av bisköldkörtelsvävnad under operation skyddande mot permanent hypokalcemi, vilket kan tala för att metoden borde användas oftare än vad som är fallet idag.

Errata

The title in the original paper I is wrong, there is written Grave disease but should be Graves´ disease.

In the original paper II on page 1134 in surgical technique it says: parathyroid glands detected preoperatively, it should be: parathyroid glands detected peroperativley .

In the original paper III on page 1935 in the text of results it says: 1,135 patients were medically treated before surgery, it should be 1,139 patients were medically treated before surgery, as in Table 1.

In the original paper III on page 1940 is it referred to Erbil et al as a reference number 25, it is unfortunately wrong reference. It should be Yamashita et al as reference number 16 instead.

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