THE IMPACT OF PARATHYROID GLAND AUTOTRANSPLANTATION DURING BILATERAL THYROID SURGERY FOR GRAVES´ DISEASE ON POSTOPERATIVE HYPOCALCAEMIA

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Objective. The aim of this study was to compare the rate of hypocalcaemia after bilateral thyroid resection for Graves' Disease in patients with and without parathyroid gland autotransplantation (PTAT).

Patients and Methods. A total of 153 patients following thyroid surgery for Graves' disease were studied. Patients were divided into three groups. Subgroup I comprised of 129 patients without PTAT, Subgroup II comprised of 19 patients with PTAT of one parathyroid gland and Subgroup III comprised of 6 patients with PTAT of two parathyroid glands. Association between PTAT and postoperative hypocalcaemia (PH) after thyroidectomy was investigated.

Results. There were 27/128 (21.1 %) patients with transient and 10/128 (7.8 %) patients with permanent hypocalcemia within Subgroup I. Among Subgroup II 4/19 (21.1 %) patients developed transient and no patient developed permanent hypocalcaemia, while in Subgroup III 2/6 (33.3 %) patients developed transient hypocalcaemia which became persistent. Thus, the frequency of permanent postthyroidectomy hypocalcaemia (PH) was significantly higher in the Subgroup III with PTAT of two parathyroid glands when compared to the Subgroup I without PTAT (p=0.032) and Subgroup II with PTAT of only one parathyroid glands (p=0.012) .

Conclusion. PTAT of one parathyroid gland is an effective procedure to reduce the incidence of permanent hypoparathyroidism after bilateral surgery for Graves disease. Transient hypoparathyroidism was not influenced by PTAT.

Key words: Graves´ disease – Hypoparathyroidism – Endocrine Ophthalmopathy – Cross sectional study – NOSPECS

In spite of significant changes that occurred in the past few decades in relation to the evolution of techniques for safe and effective surgery for Graves´ disease (GD), this is still associated with a higher rate of postoperative hypocalcaemia (PH) than that after surgery for other benign thyroid conditions (THOMUSCH et al. 2003; LAL et al. 2005; CHIANG et al. 2005). In several series, the frequency of hypocalcaemia varied from 1.6 % to more than 50 % (WINGERT et al. 1986; HERRANZ-GONZALES et al. 1991; DEMEESTER-MIRKINE et al. 1992; MCHENRY et al., 1994; SHINDO et al. 1995; PATTOU et al. 1998; KURUKAHVECIOGLU et al 2007). Haemodilution secondary to surgical stress with elevation of urinary calcium excretion (DEMEESTER-MIRKINE et al. 1992), calcitonin release and hungry bone syndrome in patients with hyperthyroidism and osteodystrophy (PATTOU et al. 1998) and autoimmune fibrosis compromising parathyroid vascularization (HERRANZ-GONZALES et al. 1991) are claimed to be potentially responsible for this phenomenon.

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In the surgeon's view, the most likely cause of PH certainly is hypoparathyroidism secondary to devascularization or inadvertent excision of one or more parathyroid glands during surgery (WINGERT et al. 1986; SHINDO et al. 1995; LEWANDOWICZ M 2007). *In situ* preservation of as much functional parathyroid tissue as possible is the key to minimizing permanent hypoparathyroidism. However, some glands may be anatomically intact but not physiologically viable, either because of thrombosis of the delicate parathyroid artery or because of parathyroid capsule edema despite meticulous dissection (DELBRIDGE et al 2002)

However, pathophysiological pathways for the development of PH after thyroid surgery for GD remain a point of discussion with the necessity for further research.

The aim of this study was to find out if the rate of permanent PH after thyroid resection for GD is related to the number of parathyroids autotransplanted in the setting of an academic teaching hospital with a special interest in endocrine surgery.

Patients and Methods

Cross-sectional study of 171 consecutive patients with GD admitted to the Department of Surgery, Philipps-University Marburg for thyroid surgery between January 1987 and January 2002 was performed. All patients were identified through the central electronic patient registry.

Data related to diagnosis and treatment of GD prior to admission, as well as early postoperative outcome were taken from the medical charts (retrospective data acquisition) and supplemented by a structured telephone interview to assess long-term outcomes (WERNER 1977; HASSAN et al. 2006). Standardized medical chart form was used to document preoperative, intraoperative and early postoperative data. This form remained unchanged through the observation period and all patients with GD were entered.

Preoperative data included biochemical and clinical thyroid status, thyroid antibodies, total serum calcium and thyroid medication.

Bilateral near total thyroidectomy was the preferred surgical procedure from 1987–1991, while between 1991 and 2000 unilateral lobectomy and contralateral subtotal thyroidectomy (Hartley-Dunhill) became the standard procedure. Since 2001, total thyroidectomy was considered superior to the other techniques. Independent of the extent of resection, a standardized surgical technique was employed comprising of visualisation and preservation of parathyroid glands with liberal handling of parathyroid autotransplantation, if insufficient blood supply was suspected due to surgical devascularization.

Surgery for Graves´ disease was performed in 171 patients in which medical treatment failed to correct hyperthyroidism. Among further indications were large thyroid size (WHO III) and/or the presence of significant or progressive endocrine ophthalmopathy. Patients were further divided into three Subgroups according to PTAT at the time of surgery. Thus, Subgroup I comprised 128 of patients without PTAT, Subgroup II comprised of 19 patients with PTAT of only one parathyroid gland and patients with PTAT of two parathyroid glands were assigned to Subgroup III.

All operations were performed or assisted first hand by consultant surgeons experienced in thyroid and parathyroid surgery.

Registered intraoperative data comprised of surgical procedure type, training status of the surgeon (consultant or trainee), weight of resected and remaining tissue and possible parathyroid autotransplantation. Data of the early postoperative period consisted of serum-calcium levels, calcium and/or vitamin D supplementation, thyroid hormone replacement therapy and length of hospital stay. For evaluation of long term follow-up, a structured telephone interview was conducted. Answers were recorded by an interviewer on a standardized clinical data registration form. Postoperative complications, specifically transient and permanent PH were registered.

PH was assumed in any patient in the need for postoperative calcium and/or vitamin D supplementation for symptomatic hypocalcaemia (paresthesia or tetany). Transient hypocalcaemia was defined as need for medical treatment for less than six months after thyroid surgery. Permanent hypocalcaemia was defined as persistent need for medical treatment over that period of time. Unfortunately, PTH-levels were not routinely obtained.

Statistical analysis. Univariate analysis (cross tables, chi-square test) was used to determine associations between the rate of permanent hypocalcaemia and existing GO as implemented in SPSS (SPSS version 12.0, Chicago, Illinois, USA). The Mann-Whitney U-Test was used to compare the rate of hypocalcaemia within the Subgroups grouped for the severity of concomitant GO. Probabilities of less than 0.05 were accepted to identify significance.

Results

Between January 1987 and January 2002, 171 patients were operated on for GD. In 153/171 patients (89

Table 1
Demographics data, surgical experience as well as postoperative hypocalcaemia after thyroid resection for GD related to PTAT.

	noPTAT (n=128)	PTAT of one Gland) (n=19)	PTAT of two Gland) (n=6)
Age (median in years)	37.9 (range 10-75)	35.7 (range 17-53)	42.21 (range 31-53)
Gender (male/female)	27/102	2/17	1/5
Transient Hypocalcemia	27	4	2
Permanent Hypocalcemia	10	0^	2**
Surgical experience (consultant/trainee)	89/39	16/3	6/0

** statistical significance at p=0.032 by comparison the permanent hypocalcaemia rate of (Subgroup III) to the group without PTAT (Subgroup I) and p= 0.010 by comparison the permanent hypocalcemia rate to the group of PTAT of only one Gland using the non parametric Mann-Whitney *U*-test.
^ no statistical significance at p=0.202 by comparison the permanent hypocalcaemia rate of the Subgroup II to the group without PTAT Subgroup I using the non parametric Mann-Whitney *U*-test.

%) complete data sets could be obtained. There were 123 women with a median age of 36 years (range 10-75) and 30 men with a median age of 33 years (range 22- 65). Length of follow-up was median 96 months postoperatively (range 12 – 216 months). 42/153 (27.5 %) patients failed to be contacted for the last follow-up. Therefore, the patient's general practitioner was contacted and asked the same set of questions to obtain the relevant data.

The level of TSH-receptor antibodies (TRAb) was preoperatively measured in 87/153 patients (56.8 %) and was found increased in 80/87 (92 %). In seven patients (8 %) the TRab level was within the normal range. In these patients clinical symptoms, measurement of endocrine orbitopathy and ultrasonography of the thyroid gland confirmed the suspected Graves´ disease.

Hypocalcaemia and parathyroid autotransplantation (PTAT). There were 128/153 (83.6 %) patients without PTAT at time of surgery (Subgroup I). In addition, 25/153 (16.3 %) patients received PTAT were further divided into a group of 19/25 patients (76 %) with PTAT of only one parathyroid gland (Subgroup II) and 6/25 patients (24 %) with PTAT of two parathyroid glands (Subgroup III). Patient characteristics (age, gender and type of resection) were similar within the three groups (Table1). Overall, there was no correlation between thyroid volume as well as TRab titers and GO (data not shown). Although the number of total thyroidectomies was low, there was no relationship between the rate of hypocalcemia and the extent of thyroid surgery in those three subgroups.

All patients had preoperative calcium values higher than 2.1 mmol/l (median 2.4; range 2.1-3.0 mmol/l). Parathyroid tissue was resected and reimplanted in 25 patients (16.3 %). In 19/24 patients (11.7 %) one and in 6/24 patients two (3.9 %) parathyroid glands were reimplanted into a pocket of the ipsilateral sternocleidomastoid muscle. Transient hypocalcaemia occurred in 33 (21.5 %) patients. The values of postoperative calcium at hospital discharge are shown in Fig. 1.

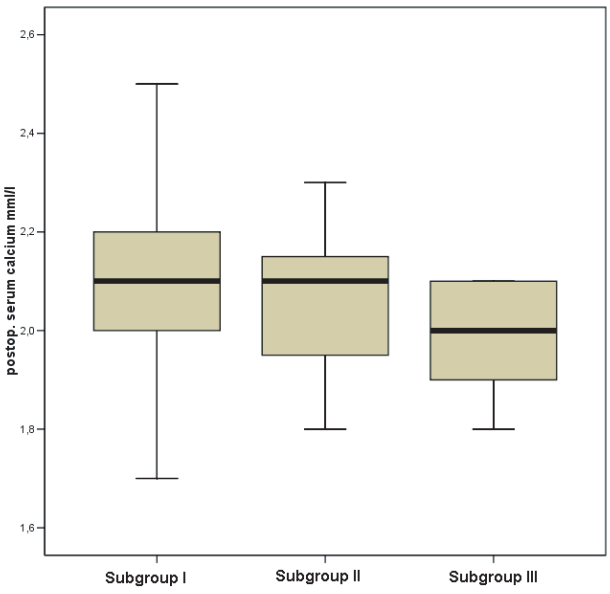

Fig. 1 Box and whisker plot (median = bar, interquartile range = box and whiskers = range) of the postoperative serum calcium level in mmol/l assessed at Hospital discharge for all Subgroups (Subgroup I: no PTAT, Subgroup II: PTAT of only one Parathyroid Gland and Subgroup III: PTAT of two Parathyroid Glands).

At follow-up, supplementation of calcium and/or vitamin D for mild hypocalcaemia was recorded in 12 patients (7.8 %). They were normocalcaemic with oral vitamin D and/or calcium at a maximum dose of 2 g daily and had no clinical symptoms of hypocalcaemia.

Transient hypocalcaemia was recorded in 27 patients (217.1 %) and persisted in ten patients (7.8 %) of Subgroup I. There were 4 patients (21.1 %) with transient and no patient with permanent hypocalcaemia in Subgroup II. Among 6 patients with PTAT of two parathyroid glands in Subgroup III there were two cases (33.3 %) with transient hypocalcaemia in which the disease persisted. The frequency of permanent PH was significantly higher in the Subgroup III with when compared to the Subgroup I without PTAT (p= 0.032) and Subgroup II (p= 0.012), while the respective difference for transient PH was not significant. However, the frequency of permanent PH between Subgroup I and Subgroup II was statistically not significant (p= 0.212).

Discussion

Despite of the era of modern and extended thyroid surgery, which has been advocated by DELBRIDGE (2003) at the end of the 20th century, PH is still a major concern following thyroid surgery for GD. It often extends the duration of hospital stay and the need for biochemical tests, and it significantly increases the overall costs of thyroidectomy. When severe, it can lead to serious complications and require intravenous therapy to alleviate the clinical symptoms (REBER and HEAT 1995).

Although hypocalcaemia reverses spontaneously in most cases, it may remain permanent when caused by irreversible injury to the parathyroid glands. Lifelong therapy and follow-up are then mandatory to avoid the subtle, but severe and potentially lethal complications of chronic hypocalcaemia (BELLAMY and KENDALL-TAYLOR 1995).

Following thyroid surgery the frequency of hypocalcaemia varied from 1.6 % to >50 % (WINGERT et al. 1986; HERRANZ-GONZALES et al. 1991; DEMEESTER-MIRKINE et al. 1992; MCHENRY et al., 1994; SHINDO et al. 1995; PATTOU et al. 1998; KU et al. 2005). In this cross sectional study, permanent hypocalcaemia was observed in 7.8 % of 153 patients undergoing bilateral thyroid surgery for GD.

It has been suggested that PTAT is a better surgical approach to prevent postoperative permanent hypoparathyroidism during thyroid surgery. In 1975, HICKEY and SAMAAN (1975) and WELLS et al (1975) showed that autotransplanted PTGs secrete PTH. To date, the success rate of PTAT during neck surgery including thyroidectomy exceeds 95 %, but it is surprising that this technique is not employed more often (BAUMANN et al 1993). Indeed, many surgeons do not perform PTAT either routinely or selectively during thyroid surgery. By contrast, KOMMISARENKO et al (2000) and ZEDENIUS et al (1999) recommend prophylactic application of routine PTAT during total thyroidectomy, reporting a decrease in permanent hypoparathyroidism to almost zero.

When considering the number of PTGs to be autotransplanted during thyroidectomy, several authors agree that one and up to two glands must be grafted. OHMAN et al (1978) and KIHARA et al (2005) compared parathyroid preservation *in situ* with routine PTAT of all visualized glands; these authors reported an incidence of 43 % and 21.4 %, respectively, for permanent hypoparathyroidism after PTAT.

Thus, we believe that PTAT should only be performed for devascularization or inadvertently removed PTGs during thyroid surgery and not routinely or including all PTGs. Besides, PALAZZO et al (2005) demonstrated that there is a correlation between the number of parathyroids transplanted and a higher incidence of temporary hypocalcemia and that the rate of permanent hypoparathyroidism was not related to the number of the glands transplanted at the time of surgery.

In this study, the rate of permanent hypoparathyroidism decreased from 7.8 % of control group to 0 % in the PTAT group of only one gland and increased to 33.3 % in the PTAT group of two glands. It must be noted, however, that the overall number of patients developing permanent hypoparathyroidism was – unfortunately - too small to obtain a meaningful statistical comparison.

Many studies have reported a high incidence of transient hypoparathyroidism following PTAT (SENAPATI et al 1991, LO C.Y. and LAM 1998, LO C.Y 2002, ABBOUD et al 2003). This study showed that postoperative transient hypocalcemia is similar- but also high- in PTAT as compared to the control patients without PTAT. Parathyroid autotransplants are unlikely to restore eucalcemia in the immediate postoperative period.

However, in the presence of difficulty in preservation of parathyroid glands as a result of anatomic variation and the fact that GD represents an autoimmune disease with higher blood flow, fragile thyroid vessels and inflammation of the retrothyroidal plane, which

may complicate the identification and preservation of the parathyroid glands, liberal routine transplantation should be performed immediately to avoid permanent hypoparathyroidism rather than leaving nonfunctioning glands in situ. In addition, the posterior aspect of the resected thyroid specimen should be inspected routinely or dissected to identify inadvertently removed parathyroid glands for reimplantation. Technically, it is a simple procedure and the process does not add substantially to the operating time.

Although the assessment of parathyroid autografts function after thyroidectomy is impractical, the resolution of temporary hypocalcemia and maintenance of long-term normocalcemia indicate that successful autografts function for patients who have undergone simultaneous PTAT (Lo C.Y. 2002). Two of patients still suffer from permanent hypoparathyroidism in the absence of the autograft function.

A prospective, randomized trial to compare the outcome of patients with and without PTAT during thyroidectomy may not be ethical or practical. Intentional removal of all parathyroid glands for autotransplantation is clearly not indicated and the variable number of parathyroid glands preserved or transplanted during the course of thyroidectomy makes the determination of successful graft function difficult (Kommisarenko et al 2000, Lo C.Y and Lam K.Y. 2001).

In summary, every effort should be made to find a reliable way to preserve parathyroid function during thyroidectomy for Graves disease and thus "each parathyroid gland has to be treated as if it would be the last one". Opinion remains divided between preservation of the parathyroid glands and their blood supply through meticulous dissection compared with routine or selective autotransplantation of parathyroid glands during thyroidectomy. Although the preservation of parathyroid glands during thyroidectomy is eligible, PTAT should be reserved for devascularized or inadvertently removed parathyroid glands to avoid permanent hypoparathyroidism. Patients undergoing simultaneous PTAT of only one gland during thyroidectomy for Graves disease have virtually low risk of having permanent hypoparathyroidism even if they have postoperative hypocalcemia.

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