HYPOCALCEMIA AFTER THYROID SURGERY SINGLE-CENTER EXPERIENCE BASED ON 987 PATIENTS OPERATED ON FOR VARIOUS THYROID DISEASES WITHIN ONE YEAR

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The aim of the study was to compare the extent of surgery in removal of thyroid tissue and serum calcium values postoperatively.

Material and methods. Between January 1 and December 31, 2005, 987 patients were operated on at our department due to various thyroid disorders. Patients with anaplastic, medullary and high-stage highly-differentiated (TNM>T3, N0, M0) thyroid carcinomas, as well as reoperated individuals, were excluded from the investigation. The patients were divided into three groups, depending on their serum calcium values; thus, the authors distinguished groups with mild (2.0-2.19 mmol/l), moderate (1.8-1.99 mmol/l) and severe hypocalcemia (<1.8 mmol/l). Differences between the groups were assessed by statistical methods (the t-Student’s test and the χ² test – the STATISTICA software). The value of p<0.05 was accepted as statistically significant.

Results. Of 987 surgical patients, 63 (6.4%) were found to have symptomatic or asymptomatic hypocalcemia. The group included 61 females and two males, their mean age being 50.1±12 years. The intensity of clinical symptoms of hypoparathyroidism was positively correlated with serum calcium values and the said symptoms were most clearly seen in patients classified as belonging to group 3 (Ca<1.8 mmol/l). The most common surgically treated thyroid disease was non-toxic nodular goiter. Hypocalcemia was the most frequent finding in patients operated on due to thyroid carcinoma. In all patients with a mild form of hypocalcemia, the onset of clinical symptoms occurred on postoperative day 2. As it follows from the analysis, there were no statistically significant differences in hypocalcemia prevalence between patients subjected to bilateral exposure of the thyroid lobes and subtotal vs. total thyroidectomy (6 (6.1%) vs 24 (7.1%) patients). On the other hand, a statistically significant difference between the lower prevalence rate of hypocalcemia in unilateral procedures (p<0.001) as compared to bilateral neck explorations (4 (1.4%) vs 59 (8.4%) patients) seems to be logical and physiologically justified. In addition, an element that was found to affect the level of calcium deficit was the number of parathyroid glands identified “in situ”. Hence, the prevalence of hypocalcemia increased with a decrease in the number of identified parathyroids (p<0.05). In hypocalcemic patients, hospitalization time ranged from 3 to 11 days, with a mean time of 5.3 days as compared to 3 days in patients without complications. Six months after the surgery and pharmacotherapy, no clinical and biochemical signs of hypocalcemia were noted in the above described group.

Conclusions. The risk of hypocalcemia following thyroid surgery is higher in bilateral neck explorations. There are no statistically significant differences in postoperative hypocalcemia between patients subjected to bilateral subtotal vs. total thyroidectomies.

Key words: hypocalcemia, complications, thyroid

Hypocalcemia is a fairly common complication of thyroid surgery. It is presently believed to be much more frequent than damage to the recurrent laryngeal nerve; according to the literature, its incidence ranges from 1.7 to 68% (1, 2). Asymptomatic hypocalcemia is defined
as a serum calcium level that is decreased below the low normal value and detected in at least two subsequent examinations. In cases of symptomatic hypocalcemia, the above definition is extended to include various clinical symptoms which are manifested with varying intensities (3). In the majority of cases, hypocalcemia is transient, yet it may also appear as a fixed form as a result of surgical treatment of thyroid diseases. At present, special emphasis is placed on early identification of patients at high risk of postoperative hypocalcemia in order to introduce early management, thus preventing development of the fully symptomatic hypoparathyroidism syndrome. Early determinations of postoperative serum calcium levels and clinical follow-up of patients are aimed at prompt identification of individuals at risk for hypocalcemia. Numerous centers have introduced monitoring of decreased serum parathormone levels in the course of strumectomies, as well as assessment of the effects of such iPTH changes on postoperative serum calcium values (1, 2, 4). Reports are published that describe attempts at postoperative hypocalcemia prevention, consisting of prophylactic administration of calcium preparations after the surgery (5). While presenting the scope of complications following thyroid surgery, a vast majority of authors stress hypocalcemia-associated prolonged hospitalization that increases the costs of treatment (6).

The aim of the study was the evaluation of postoperative changes in serum calcium levels depending on the extent of surgery resulting from various thyroid pathologies.

MATERIAL AND METHODS

Between January 1 and December 31, 2005, 987 patients were operated on at Department of Endocrine Surgery, Third Chair of General Surgery, Collegium Medicum, Jagiellonian University, due to various thyroid disorders. Patients with anaplastic, medullary and high-stage highly-differentiated (TNM>T3, N0, M0) thyroid carcinomas, as well as reoperated individuals, were excluded from the investigation. The study group consisted of 862 females (87.3%) and 125 males (12.7%) aged from 15 to 84 years (mean age, 52±14 years).

The operations included bilateral neck explorations with total or subtotal thyroidectomy, or with total lobectomy and isthmectomy and subtotal excision of the contralateral lobe. In case of lesions involving a single thyroid lobe only, the operators performed unilateral exploration with total excision of the involved lobe and an isthmectomy; the normal, contralateral lobe was left intact, without any surgical intervention. The prospective analysis of the patients was based on calcium determinations performed in the perioperative period, testing calcium levels a day before surgery and subsequent monitoring of changes in calcium values on consecutive postoperative days until the day of discharge. In all patients, the surgeons attempted to identify the parathyroid glands in situ and preserve their normal blood supply, depending on the extent of the surgery.

In the remaining cases of inadequate blood supply to the identified parathyroid glands, fragmented parathyroid parenchyma was implanted into the ipsilateral sternocleidomastoid muscle. The patients were divided into three groups, depending on their serum calcium values; thus, the authors distinguished groups with mild (2.0-2.19 mmol/l), moderate (1.8-1.99 mmol/l) and severe hypocalcemia (<1.8 mmol/l). Patients in the mild hypocalcemia group were administered oral calcium supplementation at the dose of 1000 mg/day, while the moderate group received oral calcium preparations at the dose of 1000 mg and vitamin D3, with the dose of the latter depending on calcium values. In symptomatic hypocalcemia (the moderate and severe group), IV calcium supplementation was prescribed at doses in proportion to the intensity of symptoms; the patients also received oral vitamin D3 at the dose of 2 µg/day, continued until clinical symptom resolution; they also received daily oral calcium preparations (2000 mg) and vitamin D3 (1 µg). Calcium concentration levels were determined 7 days postoperatively, after the patient had been discharged, and subsequently every 14 days until serum calcium values normalized. The patients were discharged when their serum calcium levels reached the minimum value of 2 mmol/l and the clinical symptoms of hypoparathyroidism subsided. Postoperative follow-up was continued for at least six months.

Differences between the groups were assessed by statistical methods (the t-Student’s test and the χ² test – the STATISTICA software). The value of p<0.05 was accepted as statistically significant.
RESULTS

Of the 987 surgical patients, 63 (6.4%) were found to have symptomatic or asymptomatic hypocalcemia. The group included 61 females and two males, their mean age being 50.1±12 years. The intensity of clinical symptoms of hypoparathyroidism was positively correlated with serum calcium values; these symptoms were the most clearly seen in patients classified as belonging to group 3 (Ca <1.8 mmol/l). The most common surgically treated thyroid disease was non-toxic nodular goiter. Hypocalcemia was the most frequent finding in patients operated on due to thyroid carcinoma. Tables 1 and 2 present numerical and percentage data on the types of thyroid pathologies and the prevalence of hypocalcemia.

In all patients with a mild form of hypocalcemia, the onset of clinical symptoms occurred on postoperative day 2. On the other hand, patients with moderate and severe calcium deficits had symptoms that were much more frequently manifested on the first day after the operation. Detailed data are presented in fig. 1, while fig. 2 illustrates the dynamics of the serum calcium increase in subsequent postoperative days.

As it has been mentioned previously, the patients were subjected to various procedures, starting from unilateral neck exploration with lobectomy and isthmectomy and ending with bilateral exposure of the thyroid lobes, followed by total or subtotal thyroidectomy, or total lobectomy with isthmectomy combined with subtotal resection of the contralateral lobe. The prevalence of hypocalcemia depended on the thyroid pathology and on the extent of surgery; this is presented in tab. 3. As it follows from the analysis, there were no statistically significant differences in hypocalcemia prevalence between patients subjected to bilateral exposure of the thyroid lobes and subtotal vs. total thyroidectomy (6 (6.1%) vs 24 (7.1%) patients). On the other hand, a statistically significant difference between the lower prevalence rate of hypocalcemia in unilateral procedures (p<0.001) as compared to bilateral neck explorations (4 (1.4%) vs 59 (8.4%) patients) seems to be logical and physiologically justified.

While analyzing the material of surgical patients with respect to thyroid pathologies, the authors observed that hypocalcemia was stati-
In addition, an element that was found to affect the extent of calcium deficit was the number of parathyroid glands identified “in situ”. Hence, the prevalence of hypocalcemia increased with a decrease in the number of identified parathyroids (p<0.05). The results are presented in tab. 4.

Autotransplantations were performed in 97 (9.8%) patients in whom parathyroids had been identified in the resected material and fewer than two glands had been seen intraoperatively. In this group, hypocalcemia was noted in 12 patients. The minimum period of calcium supplementation was 7 days in one female with a mild form of hypocalcemia. In turn, the longest period of treatment was required by another female with a severe form of hypocalcemia, in whom calcium supplementation and vitamin D₃ administration lasted for 97 and 83 days, respectively. The mean duration of supplementation was 24 days.

In hypocalcemic patients, hospitalization time ranged from 3 to 11 days, with the mean time of 5.3 days as compared to 3 days in patients without complications. Six months after

Table 3. Hypocalcemia depending on thyroid pathology and the scope of surgery

<table>
<thead>
<tr>
<th>Hypocalcemia</th>
<th>diagnosis</th>
<th>symptomatic</th>
<th>asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thyroidecotomy</td>
<td>TC</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>G-B</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>SN</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>SNT</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total lobectomy with isthmectomy and partial contralateral lobectomy</td>
<td>TC</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>G-B</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>SN</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>SNT</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Subtotal bilateral lobectomy</td>
<td>TC</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>G-B</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>SN</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>SNT</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Unilateral lobectomy</td>
<td>TC</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>G-B</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>SN</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>SNT</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

TC – thyroid carcinoma, G-B – Graves’ disease, SN – nodular goiter, SNT – toxic nodular goiter

Table 4. Hypocalcemia depending on the number of identified parathyroids in situ

<table>
<thead>
<tr>
<th>Liczba zidentyfikowanych przytarczy in situ / No. of identified parathyroids in situ</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liczba chorych / no. of patients</td>
<td>398</td>
<td>221</td>
<td>160</td>
<td>117</td>
<td>91</td>
</tr>
<tr>
<td>Hipokalcemia / hypocalcemia</td>
<td>15</td>
<td>11</td>
<td>13</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>% hipokalemii / % of hypocalcemia</td>
<td>3,76</td>
<td>4,98</td>
<td>8,12</td>
<td>12,8</td>
<td>9,89</td>
</tr>
</tbody>
</table>
the surgery and pharmacotherapy, no clinical or biochemical signs of hypocalcemia were noted in the above described group.

DISCUSSION

The incidence of complications in thyroid surgery as compared to other general surgery procedures is rather low. Nevertheless, complications do occur, the most common being postoperative hypocalcemia. In the presented group of 987 surgical patients with various thyroid diseases, transient hypocalcemia was observed in 6.4% of the individuals. No fixed hypocalcemia was noted in any of the patients. The above data are in accord with reports published worldwide, although there are surgical centers where the reported percentage of transient hypocalcemia was 68%. Fixed hypoparathyroidism is defined as absence of normal serum calcium concentration levels seen 1 year postoperatively, along with persisting clinical symptoms. According to the literature, its percentage ranges from a fraction to several per cent, usually not exceeding 3%. Some authors suggest, however, that early postoperative hypocalcemia may be a consequence of perioperative hemodilution (1-4, 6-9).

In the present study, clinical symptoms of hypocalcemia have been observed in 27 (42.8%) patients from the moderate and severe group. No clinical symptoms were noted in patients with a mild form of the condition. Symptoms have been most commonly observed on day 1 and 2 postoperatively, along with persisting clinical symptoms. According to the literature, its percentage ranges from a fraction to several per cent, usually not exceeding 3%. Some authors suggest, however, that early postoperative hypocalcemia may be a consequence of perioperative hemodilution (1-4, 6-9).

The literature worldwide does not provide a uniform position as to the incidence of hypocalcemia depending on the scope of the surgical procedure. However, the necessity of identifying and preserving in situ the greatest possible number of parathyroids is emphasized, as is the need for possible early parathyroid autotransplantation. Various authors also stress the fact that in referral centers performing total thyroidectomies due to thyroid carcinoma, multinodular goiter and autoimmune thyroid diseases, the incidence of complications generally does not depend on the scope of the procedure in bilateral lobectomies (3, 7, 8, 10, 11). The emphasis is placed on the need for precise and, if possible, bloodless surgical techniques, preserving the vasculature of the parathyroids (9, 11, 12).

The present authors have deemed it worthwhile to compare the prevalence of hypocalcemia following subtotal bilateral thyroidectomies. For many years, this procedure was believed to be safe and a golden method allowing for avoidance of not only hypocalcemia, but also damage to the laryngeal nerves with hypocalcemia rates similar to those following total thyroidectomies; this procedure is nowadays much more commonly performed, not only for thyroid carcinomas, but also for multinodular goiter and Graves’ disease. The study has demonstrated lack of significant difference in the prevalence of hypocalcemia in both groups. Similar data was reported by Alimoglu et al., Bellantone et al. and Pappalardo et al. (3, 12, 13). These authors stress the presence of complications following bilateral subtotal thyroid resections. In the present investigation, hypocalcemia has been most commonly noted in patients with thyroid carcinoma. Similar observations were made by Quiros, who suggested that a neoplastic process involving the thyroid gland may itself be a factor, indicating a patient at risk for postoperative hypocalcemia (2). The present authors have also noted the condition to occur more frequently in hyperthyroidic patients, which has been reported by other authors (6). As it could be expected, hypocalcemia is much less common after unilateral neck explorations and this observation is also confirmed by the literature (1, 2, 3). There is no consensus among various authors as to the number of parathyroids that have to be preserved in situ to prevent the patient from developing hypocalcemia. The majority of investigators believe the safe number to be two parathyroid glands with intact blood supply. Nevertheless, opinions are also voiced that “a single normal parathyroid gland is capable of providing appropriate calcium-phosphate metabolism” (7).

Another important issue addressed in the literature is the occurrence of hypocalcemia, both asymptomatic and symptomatic, in post-parathyroid autotransplantation patients; the rate is in excess of 60% of cases in the autotransplantation group. Unfortunately, no details on the number of parathyroids left in situ and autotransplanted in those patients are available (1).

An increasing number of authors advocate the need for intraoperative iPTH monitoring, which is now standard in parathyroid surgery.
and aims at early identification of patients at risk of hypoparathyroidism in the postoperative period. Those in favor of such management raise the argument that in the majority of cases, this method allows for prevention of symptomatic hypocalcemia and shortening of the mean hospitalization time to the necessary minimum, continuing monitoring only of patients in whom hypocalcemia is most likely to occur, and discharging the remaining individuals within 48 hours postoperatively, at the maximum. To date, the obligatory standard dictates close monitoring of serum calcium levels. However frequently, the observation should be carried out for as long as 48 hours to identify patients at risk of hypocalcemia. Within this period, calcium levels show the greatest decrease, which has been also observed in the present study. In the opinion of the present authors, although the results of intraoperative iPTH monitoring are promising, the cost per patient is still high and this fact will be a decisive factor in abandoning this management method (1, 2, 4).

On the other hand, today, when treatment costs are scrupulously calculated and emphasis is placed on maximally shortening hospitalization, it may turn out that in even considering the cost of iPTH determination, the expenditure per capita when employing the test may be lower when compared to unjustified prolonged hospitalization in the majority of patients. In addition, as has been pointed out by Dotzenrath, hypocalcemia may be monitored on an outpatient basis in most patients (4,6). Similarly, the present authors have observed that a higher number of identified parathyroids with appropriate blood supply left in situ has been associated with a lower percentage of postoperative hyperparathyroidism (2, 3, 5).

In the investigated group, autotransplantations have been performed less frequently as compared to reports from the literature, which may be associated with a worldwide tendency to perform at least one parathyroid autotransplantation in cases when appropriate blood supply of the parathyroid gland is dubious or difficult to assess. This may result in some parathyroids being autotransplanted unnecessarily, triggering equally unnecessary consequences of transient hypocalcemia (1, 2, 4).

In the present study, hospitalization time has not differed significantly from data presented by other authors, while the duration of postoperative calcium supplementation has been markedly shorter, ranging from 7 to 97 days, with the mean value of 24 days (4, 6). Reports are published that suggest preventive administration of oral calcium preparations to all patients operated on for goiter in order to prevent hypocalcemia. In turn, arguments are also proposed that point to unwarranted treatment employed in numerous patients and its related costs (1, 2, 4, 8, 10). Investigations have been also performed that bring the issue of prophylactics even further, studying the role of a standard postoperative single intravenous dose of calcium and emphasizing the benefits of employing such a management method in patients subjected to total thyroidectomies for a relatively low cost (5).

**CONCLUSIONS**

1. The risk of hypocalcemia following thyroid surgery is higher in bilateral neck explorations, operations for toxic goiter, and in cases when fewer than two parathyroid glands have been visualized.
2. There are no statistically significant differences in postoperative hypocalcemia between patients subjected to bilateral subtotal vs. total thyroidectomies.
3. Hypocalcemia generates an increased cost of treatment associated with prolonged hospitalization.

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