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Assessing Thyroid Size as an Independent Risk Factor in Thyroidectomy

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Abstract:

Background: Rates of complications of thyroidectomy, mainly hypocalcemia and recurrent laryngeal nerve injury, can be higher in certain patient groups. There are several risk factors for complications published in the literature, among them are malignancy, bilateral resection, younger age, and Grave's disease.[4,5] To our knowledge, there is not a study that examines the role of thyroid size as an independent risk factor in total thyroidectomy.

Methods: A case-control study carried out at a tertiary, academic medical center involving patients who underwent total thyroidectomy between August, 2001 and March 2005. Pathology reports were reviewed for gland weight, size and histology, and anesthesiology reports were reviewed for estimated blood loss (EBL), American Society of Anesthesiologist score (ASA) classification and duration of surgery. Hard copies of charts were reviewed for calcium replacement as well as for length of hospital stay.

Results: Thyroid size had a positive correlation of 0.34 (N = 49) (P = 0.02) with length of surgery and 0.32 correlation (P = 0.04) between increasing thyroid size and increased hospital stay. Thyroid weight (N = 50) had a positive correlation of 0.47 (P<0.001) with estimated blood loss as did thyroid volume (N = 51) with a similar correlation of 0.49 (P<0.001). The correlation with calcium nadirs was found to be –0.27 (P= 0.05). Hypocalcemia symptoms occurred in 13.4% of patients (N=7), all of which were female, otherwise age, BMI and thyroid weight and dimensions were statistically insignificant.

Drain output is positively correlated as well with thyroid weight and dimension, 0.39 for weight (P=0.008) and 0.40 for dimension (P=0.006). Overall, 40 % of patients (N=21) had ionized calcium values below 1.0 mmol/L. Recurrent laryngeal nerve injury (N=2) occurred in 3.9%.

Conclusion: Increased thyroid size does appear to portend and increase in peri-operative complications including increased blood loss, lower hypocalcemia nadirs and overall number of complications. There is also a positive correlation with time spent in surgery, and days spent in the hospital.

Introduction: Major complications arising during thyroidectomy occur in fewer than 5% of cases (4). The most common complications are hypocalcemia and damage of the recurrent laryngeal nerve. Numerous develops over the years have helped to reduce the frequency of these complications which usually arise secondary to mechanical trauma to the glandular structures of the parathyroids or to the nerve itself during resection of the thyroid. In the case of the parathyroid glands, devascularization as well as inadvertent excision are potential, if not primary, causes. Several factors are considered to portend an increase in the rate of occurrence of complications, as is explored later in the article. The primary pre-operative factor that we examine is the actual mass of the thyroid gland and how it affects the patient peri- and post-operatively. Analysis of hypocalcemia nadir, length of hospital stay, length of surgery, the requirement for intravenous or oral calcium replacement, and the need for drains, in relation to the mass of the thyroid are examined in terms of having either a positive or negative correlation with gland size.

Patients and Methods: To determine the weight of the thyroid as an independent risk factor we performed a retrospective chart review of our patients who underwent total thyroidectomy. Between August, 2001 and March, 2005 the charts of 54 consecutive patients were reviewed, however, for two of the patients thyroid gland weight was not available thus a data set of 52 patients was used.

Background data was gathered on age, sex, and body mass index (BMI). Surgical reports were reviewed for the usage and type of drains, and occurrence of complication. Anesthesiology reports were reviewed for estimated blood loss, ASA score, and length of surgery. Nearly all patients received fine needle aspiration and ultrasound of the neck prior to surgery.

Patients' inpatient and clinic charts which included all medications administered during hospitalization were reviewed to ascertain whether calcium supplementation was implemented, as well as to determine if a patient demonstrated symptoms of hypocalcemia (parasthesias, or muscle spasms, including positive Chvostek's sign). The computerized hospital record, Citrix Powerchart, was used to determine ionized calcium nadir, and length of hospital stay. Finally, review of pathology reports yielded histological diagnosis and gland weight.

All but four of the cases were carried out by experienced Head and Neck surgeons. The remaining four cases were performed by experienced General surgeons. There was no statistical significance found between the Head and Neck surgeons' patients (N=46) versus General surgeons' patients (N=4) other than the mean and median gland weight being larger in the case of the former, 76 versus 18gm for mean, and 34 and 10gm for median, respectively (P=0.04) **see table 1.**

Statistical analysis was carried out by Betty Skipper using SAS Version 9.1 software (SAS Institute, Inc., Cary, NC.). For comparing the association between two categorical variables Fisher's exact test was used. For comparing a categorical variable with a continuous variable the Wilcoxon Rank Sum test was used. The Wilcoxon Rank Sum test was used instead of the t-test because the variables are not normally distributed. For comparing two continuous variables the Spearman correlation coefficient was used instead of the Pearson correlation because, once again, the variables are not normally distributed with regards to thyroid gland weight.

Results:

No fatalities were reported in our study group. Overall, there were two documented RLN transections, three hematomas, seven post-operative voice complaints, two tracheotomies, and one documented parathyroid devascularization with subsequent autotransplantation to SCM. Thyroid weight was greater in those with all cause complications by a factor of 2.85 (N=7)(P=0.04) The following are more specific explanations of particular complications or post-operative changes.

Calcium: biochemical markers and symptoms

The gland weight of 52 patients was compared to post-operative ionized calcium levels from the inpatient period following surgery. The correlation was found to be –0.27 (P= 0.05) which represents a slight negative relationship meaning that as thyroid weight increases the hypocalcemia nadir decreases. Interestingly, both age and BMI had positive correlations, although neither reached statistical significance, with ionized calcium nadir, meaning that as patients' age advanced and their BMI increased their degree of

hypocalcemia was somehow mitigated. Additionally, we observed whether thyroid weight had any relationship to the need for calcium replacement. It appears as though in the group that required calcium the mean size of thyroid was much larger than in the group that did not, 114 grams (gm) (N = 19, SD = 157, P = 0.12) as compared to 44 gm (N = 32, SD = 49, P = 0.12), respectively. Additionally, those requiring intravenous (IV) calcium (which was often combined with oral calcium replacement) versus solely oral calcium replacement tended to have a corresponding four-fold increase in thyroid size, 168 gm (N = 11, SD = 188, P = 0.08) as compared to 40 gm (N = 8, SD = 43, P = 0.08). Similarly, the median gland weight in the IV group was increased approximately four-fold over the oral group, 121 gm versus 29 gm (P = 0.08). In a similar comparison, patients exhibiting hypocalcemic symptoms (perioral, hand or feet numbness/parasthesias) were found to have a mean gland weight of 102 grams (N=7)(P = 0.18) as compared to those without symptoms whose mean gland weight was 66 grams (N=43)(P = 0.18). Interestingly, every patient that exhibited symptomatic hypocalcemia was female, which is in keeping with other studies that note an increased sex related risk factor for this complication. In Prim et al this is illustrated and surmised to have some correlation with perhaps a lower basal calcium level in females resulting in symptoms with smaller perturbations in calcium levels.[10] The median gland weight for these two groups was 31 grams for those without symptoms and 94 grams for those who were symptomatic (P = 0.18). At six months there were no remaining patients with complaints of hypocalcemia. Thus, it appears as though all increased morbidity of the larger thyroid group is relatively transient in terms of hypocalcemia.

Length of Surgery

For evaluating the length of surgery, a Spearman correlation coefficient was again used for the highly skewed distribution of gland weights. The relationship between gland weight and length of surgery showed a positive correlation of 0.34 (P = 0.02)(N = 49). Evident here is that as the weight of the gland increases so does the length of surgery. Age (N =51) actually had a very slight negative correlation,-0.11 (P = 0.45), and BMI (N = 48) had only a very slight positive correlation with length of surgery, 0.09 (P = 0.56). Actual gland volume, as determined from dimensions in pathology reports, had a significant positive correlation of 0.39 (P = 0.005) with the length of surgery. From the above it is perhaps possible to extrapolate that the size of the gland itself and not just body habitus lead to a longer and, for all intents and purposes, a more difficult surgery.

Length of Hospital Stay and Drains

In the matter of length of hospital stay several factors admittedly come into play and parsing out what contributes to extending a stay is difficult. In the four patients that did not receive drains there was a mean hospital stay of 2.2 days (SD = 1.3) and median of 2 days (Range = 1,4). In the group (N = 46) that did receive drains (the vast majority of which were Jackson-Pratt either 7mm or 10 mm, single or paired) the mean and median were 5.7 (SD = 9.0) and 3 (1,55), respectively. What then becomes a question is the patient's pre-operative status and what potential role other co-morbidities play in hospitalization duration, and for this we compiled ASA classifications on all patients. In the group of 46 who had drains, 2 were ASA class 4 and the remainder was a mixture of class 1, 2 and 3. By dropping the class 4's from the group with drains we see a 0.32 correlation (P = 0.04) between increasing thyroid size and increased hospital stay. More

about hospital stay is discussed below in the Multivariate Analysis section. In terms of drain output, which has a direct effect on the duration that drains are kept in place, there was a 0.39 correlation with thyroid weight (P=0.008) and a 0.040 correlation with gland volume (P=0.006). **See table 2.**

Estimated Blood Loss

Both thyroid weight and volume seemed to highly correlate with increased estimated blood loss (EBL). Thyroid weight (N = 50) had a positive correlation of 0.47 (P<0.001), and thyroid volume (N = 51) had a similar correlation of 0.49 (P<0.001). The correlation with BMI (N = 49) was of a much lesser extent, 0.25 (P = 0.09), and that of age (N = 50), interestingly, turned into a negative correlation of -0.11 (P = 0.44). The latter two factors, of note, did not reach statistical significance. Again, there is a strong correlation here with blood loss as there is with length of surgery that implicates the gland size more strongly than it does the patient's BMI, or habitus.

Recurrent Laryngeal Nerve Injury

Due to the relatively small number of RLN injuries (N=2), no analysis is able to reach statistical significance. In terms of voice complaints, however, BMI reached statistical significance in those having voice complaints. In those patients with voice complaints (N=7), the mean BMI was 36.2 (SD=8.2) as compared to patients without complaints (N=42) who had a BMI mean of 28.6 (P=0.02). Likewise, the median for with and without complaints was 35 (26,51) versus 27 (17, 50)(P=0.02), respectively. **See Table 4.**

Multivariate Analysis

By using multivariate analysis where estimates of length of stay are based on ASA class, presence of drain(s), and thyroid weight the following was found. Length of stay was determined using geometric means to help correct for the skewed distribution of thyroid weights and duration of hospital stays. In short, logs were taken of all length of stay values in days so that a more bell-shaped curve could be achieved, and then the antilog values were used to get more interpretable numbers. In using multivariate analysis here we are able to adjust for differences in ASA class and perhaps obtain a more accurate depiction of the bearing of thyroid weight independently on hospital stay. Multivariate analysis in which the class 4 patients were excluded and the class 1 and 2 patients were combined shows that once a thyroid is greater than or equal to 80 gm the length of stay increased 37% over thyroids of lesser weight ($P = 0.10$). A patient's ASA class appeared to have less of an impact on length of stay between the two groups, 1 and 2 being the first group and 3's being the second. Only 0.5 days was added to the latter group's stay ($P = 0.40$).

Discussion:

Complication rates for total thyroidectomy have decreased significantly from its advent which supposedly came at the hands of Albucasis in Spain some time before his death in 1013 A.D, and later promulgated by Theodore Kocher and William Halstead.[5,10]

The most recent era, defined as the period since 1995, has seen dramatic improvements still, where permanent RLN palsy incidence is somewhere between 0.3 and 2.3% and permanent hypoparathyroidism is somewhere between 0.7 and 3% as compared to 14% and 29%, respectively, prior to this era.[1,5,10] The literature advocates that total thyroidectomy is increasingly favored for not only the main indications of presence of suspicious thyroid nodules and malignancy, but also for multinodular goiter and Grave's disease as complication rates are decreasing relative to the risks of re-operative surgery in the latter cases of MNG and Grave's disease.[5,11-13] In Serpell's series, they found that in primary operations for goiters there was no increased risk of permanent hypoparathyroidism in total thyroidectomy (TT) as compared to subtotal thyroidectomy (STT), so regardless of the theoretical risk of re-operation which is anywhere from 5-20 times that of primary surgery, there is no justification for STT.[5] Similarly, with regards to RLN palsy occurring at a rate of 0.3% following TT in their series, and their citing of that rate increasing to between 3 and 18% upon re-operation for recurrent goiter, which occurs in 30-50% of less than total procedures, it is obvious that TT carries a lower risk in the long run.[5,15] The above is testament that total thyroidectomy continues to be an effective therapy while complication rates continue to decline.

Overwhelmingly, two factors are cited as being the best prevention of hypocalcemia and RLN palsy in the post-operative period: a thorough knowledge of the anatomy, and meticulous surgical technique.[10] The etiologies of postoperative hypocalcemia include surgical trauma, or as one author calls it, "overzealous manipulation," devascularization or inadvertent excision of the parathyroid glands.[4,10] The preservation of the inferior thyroid artery which supplies the inferior parathyroid

glands is critical, and any suggestion that this supply might be compromised should lead to autotransplantation of at least one gland into the ipsilateral sternocleidomastoid with calcium and vitamin D supplementation post-operatively as this has been shown to greatly reduce permanent hypoparathyroidism and subsequent hypocalcemia.[4,10] As our analysis shows, a gland's weight (and volume) independently increases the length of surgery, EBL and correlates positively with increased severity of hypocalcemia. It is possible to take into account the possible traumatic causes and presume that for a longer (more manipulation of thyroid and parathyroids) and more difficult (increased blood loss and possibly increased risk of vascular trauma ie. Inferior Thyroid artery) surgery, size of the gland does seem to be the central issue.

In Sippel et al, risk factors for incidental parathyriodectomy and the occurrence of hypocalcemia were evaluated. Apparent risk factors for incidental removal of parathyroid glands were younger age, bilateral resection, and malignant pathology; however those factors apparently having no increase for this complication were sex, presence of goiter, thyroid gland weight, and re-operation on the neck.[4] Analysis of these latter factors that supposedly do not portend operative complications did not reach statistical significance (notably, P=0.208 for gland weight).[4] This study is mentioned because it is one of very few to isolate thyroid gland weight as a variable. In our study, statistically significant correlations were found between thyroid weight (and dimension) and increased length of hospital stay (P = 0.002), time spent in surgery (P = 0.02), drain output (P = 0.008), length of ionized calcium monitoring (P = 0.004), and estimated blood loss (P = <0.001) **see Table 1**. Gender was only statistically significant in so far as

only women exhibited symptomatic hypocalcemia, as noted above. In multivariate analysis of ASA class, thyroid weight and length of stay, statistical significance was lost.

In our series there were seven reported complications out of 51 cases for a rate of 13.7%. In patients with reported complications, thyroid size was 2.85 times that of those in whom there was no mention of complications in the operative report. The mean gland size in the complication group was 348 gm as opposed to 122 gm in the no complication group. Likewise, the median gland size in the complication group was 220 gm as opposed to 63 gm (P = 0.04) **see table 2**.

Table 1

Variable	Type of Surgeon		p-value
	Head and Neck	General	
Thyroid weight			
N	46	4	
Mean (SD)	76 (112)	18 (18)	
Median (Range)	34 (8, 660)	10 (6, 44)	0.04
Estimated Blood Loss			
N	48	4	
Mean (SD)	180 (243)	218 (203)	
Median (Range)	100 (10, 1400)	175 (20, 500)	0.61
Hypocalcemia nadir			
N	48	4	
Mean (SD)	1.00 (0.09)	1.10 (0.08)	
Median (Range)	1.02 (0.78, 1.16)	1.12 (0.99, 1.17)	0.06

Table 2: Spearman correlations between continuous variables

Variable	Age	BMI	Thyroid Weight	Thyroid dimension
Length of stay days				
N	52	49	50	51
Correlation	0.21	0.05	0.43	0.41
p-value	0.13	0.74	0.002	0.002
Periop surgery time				
N	51	48	49	50

Correlation	-0.11	0.09	0.34	0.39
p-value	0.45	0.56	0.02	0.005
Drain output				
N	48	46	46	47
Correlation	-0.03	0.15	0.39	0.40
p-value	0.84	0.31	0.008	0.006
Ionized calcium length of monitoring				
N	52	49	50	51
Correlation	0.16	0.05	0.40	0.35
p-value	0.26	0.71	0.004	0.02
Hypocalcemia nadir				
N	52	49	50	51
Correlation	0.11	0.30	-0.28	-0.24
p-value	0.42	0.82	0.047	0.10
Estimated blood loss				
N	52	49	50	51
Correlation	-0.11	0.25	0.47	0.49
p-value	0.44	0.09	<0.001	<0.001
Length of follow-up (weeks)				
N	52	49	50	51
Correlation	0.27	0.16	0.14	0.14
p-value	0.05	0.28	0.33	0.33

Table 3: Association of age, BMI, gland weight, and gland dimension with complications – in op report

	Complications – in op report		
Variable	No	Yes	p-value
Age			0.76
N	45	7	
Mean (SD)	45.9 (17.5)	44.4 (17.4)	
Median (Range)	47 (11, 82)	45 (19, 75)	
BMI			0.41
N	43	6	
Mean (SD)	29.4 (8.1)	31.9 (8.7)	
Median (Range)	28 (17, 51)	31 (23, 46)	
Thyroid weight			0.06
N	43	7	
Mean (SD)	54 (66)	172 (226)	
Median (Range)	30 (6, 314)	94 (9, 660)	
Thyroid dimension			0.04
N	44	7	
Mean (SD)	122 (162)	348 (397)	
Median (Range)	63 (14, 784)	220 (20, 1170)	

Table 4

Variable	Voice		p-value
	No	Yes	
Age			0.51
N	45	7	
Mean (SD)	44.8 (17.0)	51.1 (19.3)	
Median (Range)	47 (11, 79)	45 (31, 82)	
BMI			0.02
N	42	7	
Mean (SD)	28.6 (7.6)	36.2 (8.2)	
Median (Range)	27 (17, 50)	35 (26, 51)	
Thyroid weight			0.38
N	43	7	
Mean (SD)	72 (115)	66 (50)	
Median (Range)	31 (6, 660)	44 (20, 141)	
Thyroid dimension			0.32
N	44	7	
Mean (SD)	154 (232)	142 (101)	
Median (Range)	67 (14, 1170)	79 (45, 266)	

Unlike Sippel's study, only total thyroidectomy patients were included in this study, and therefore unilateral and bilateral procedures cannot be compared. Additionally, recurrence of tumor or MNG was not collected and was not the focus of this study. Recurrence therefore cannot be assessed.

The incidence of transient hypocalcaemia after thyroid surgery in the published work varies from 1.6 to 50%, with permanent hypocalcaemia secondary to hypoparathyroidism occurring in 1.5–4%. Theoretically, resection of one normal parathyroid should not affect serum calcium levels because of the presence of typically three other normal functioning glands, however as few as two and as many as eight glands have been observedThe effects of inadvertent parathyroid excision on postoperative calcium levels and symptomatic hypocalcaemia have not been clearly characterized.[4] There are two cell types in the parathyroid gland, but only the Chief cell has the clear function of producing parathyroid hormone (PTH). In secreted form PTH,

is a straight chain peptide of 84 amino acids. PTH is synthesized continuously, but the gland stores little hormone; only enough to sustain maximal secretion rates for about 90 minutes (8). The 84 amino acid form of the hormone is the only active form and has a half-life of 2-4 minutes (8).

The occurrence of RLN palsy at a rate of 3.9% (N=2) and of transient hypocalcemia 40 %(N= 21), as defined by ionized calcium less than 1.0 mmol/L in our series parallels rates in the literature. In both patients with RLN damage, benign pathology was found.

Conclusions: Increased thyroid size appears to impact several factors including length of surgery, drain output, length of hospital stay and estimated blood loss and possibly with the degree of hypocalcemia in the peri-operative period following total thyroidectomy independent of other factors including gender, age, and BMI. Female gender seems highly correlated with experiencing hypocalcemia symptoms.

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