In situ preservation of the parathyroid glands in total thyroidectomy: a propensity score matched analysis


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Total thyroidectomy with “no-touch” parathyroid: a propensity score matched analysis

AIM: Severe hypocalcemia due to parathyroid gland damage may be a serious complication after thyroidectomy. In order to save parathyroid integrity we developed a no-touch parathyroid (NTP) thyroidectomy technique.

METHODS: We performed a total extracapsular thyroidectomy with NTP technique in consecutive 50 cases of benign goiter between July 2014 and June 2015. Parathyroid glands were firstly indentified, then they were separated from the thyroid avoiding manipulation or trauma and preserving their vascularization. Traditional scissors were preferentially used for dissection around the glands. Patients operated with NTP technique were matched by a propensity score to a control group.

RESULTS: NTP was feasible in all foreseen patients except one. Propensity score selected a group of 23 patients/group for matching. No mortality has been observed in either group. Operative time were comparable between groups. Blood loss were significantly less abundant in the NTP group. No laryngeal permanent paralysis was experienced. Hospital stay was shorter yet not significantly in NTP group. Neither hypocalcemic crisis nor permanent hypoparathyroidism were described in either group. Serum calcium levels (NTP Vs control) were significantly higher in NTP group at day 1 (p=0.03) and day 2 (p=0.002), respectively. Similarly, intact parathormone dosages were significantly higher at day 1 (p=0.004) and day 7 (p=0.001), respectively.

CONCLUSIONS: We conclude that NTP thyroidectomy is a feasible in the majority of the patients and, allows a significant reduction of blood loss without prolonging the operative time. After the procedure both values of calcemia and intact parathormonewere stable and no hypocalcemic crisis was experienced.

KEY WORDS: Parathyroid, Hypoparathyroidism, Hypocalcemia, Total thyroidectomy

Introduction

Postoperative hypocalcemia is the most common complication of total thyroidectomy 1-4. Its incidence varies between 30% and 60% due to the different criteria used to define it 3-5. It is not always associated with accompanying symptoms, and in most cases it disappears in less than 6 months 6,7. Multiple factors have been associated with an increased risk of hypocalcemia, and there are several procedures aimed at quickly identifying those patients who may develop hypocalcemia secondary to treatment 8-13. The factors associated with an increased risk of postoperative hypocalcemia include gender, type of intervention, base condition and more specifically reasons related to parathyroid damages or "stupor" due to intraoperative manipulation 14. The "no touch" parathyroid (NTP) thyroidectomy is a surgical trick developed in our center aimed at avoiding any manipulation of the
parathyroid gland during dissection. The purpose of this propensity score investigation was to verify if the incidence of hypocalcemia secondary to total thyroidectomy may be reduced with NTP technique.

**Materials and Methods**

We performed a first-time total extracapsular thyroidectomy with NTP technique in consecutive 50 cases of benign goiter between July 2014 and June 2015. The project was submitted and approved by the Internal Review Board of our Institution. All patients released fully informed consent to the procedure. Exclusion criteria were previous thyroid surgery, preoperative evidence of thyroid neoplasm.

**NTP Technique**

All procedures were performed under general anesthesia by some of the authors (VA, FR), assisted by 1 surgeon and 1 scrub nurse. The main technical rules for parathyroid glands preservation are summarized in Fig. 1. Parathyroid glands were preserved approaching them from the antivascular pole, freeing and lowering their body with a scissor avoiding to touch or press, and preserving their vascularization even—when necessary—with the interruption of the thyroid capsule. The Harmonic Focus ultrasonic shears® (Ethicon, Endosurgery Inc, USA) were the only device used, except for the purposes of parathyroid gland and recurrent laryngeal nerve preservation. Nerve monitoring was performed in all cases (NIM-ResponseR 2; Medtronic Xomed Inc, Jacksonville, FL, USA). Dissection commenced from the middle thyroid vein, followed by division of the superior pole, where the anterior and the main superior artery trunk are divided proximally to the gland capsule. After identification of the parathyroid glands and recurrent laryngeal nerves, the inferior pole was divided, with peripheral iuxta-capsular interruption of the branches of the inferior thyroid artery. The thyroid gland was then freed from its posterior vascular attachments. If one of the parathyroid glands appeared to be damaged or accidentally removed, autotransplantation was performed into the sternocleidomastoid muscle.

At the end of the thyroidectomy, the thyroid bed was washed with a saline solution at about 35°C. Drainage was systematically left in place before closing the wound. Hemostatic sponges coated with human coagulation factors fibrinogen and thrombin (TachoSil; Nycomed Austria GmbH, Linz, Austria) were applied according to the surgeon’s judgment, mainly close to the recurrent laryngeal nerve bed. The strap muscles were approximated using 3 to 4 stitches. The skin incision was closed with a subcuticular absorbable monofilament suture (Polyglactic acid 3-0 MH-1; Ethicon, Inc, Somerville, NJ, USA).

**Study design**

This is a study based on a single-center, prospectively collected, clinical database of consecutive patients whose number was considered satisfactory according to the size of previous pilot studies. These patients were matched with patients operated in the same institution by the same surgeons according to the classic-elsewhere described-technique, in the period January 2014-June 2014. In order to assemble comparable groups, we used propensity score matching. After estimating the propensity score of patients in the NTP group, we matched each patient sequentially to a patient in the control group who had the closest propensity score using simple 1:1 nearest neighbor matching. We imposed a caliper of 0.20 of the standard deviation of the logit of the propensity score.

Variables selected for case-to-case matching were age, sex, mass body index, pathologic findings (colloid Vs thyroiditis Vs hyperthyroidism), goiter volume and preoperative levels of serum calcium and intact parathormone (IPTH).

**Postoperative Dosages**

Serum calcium was measured 24 hours after surgery and routinely repeated at day 2, 7, and then monthly for the first year. Postoperative hypocalcemia was defined as a serum calcium level of less than 8mg/dL after 24 hours. In these cases therapy with calcium (1.5-3g/day) and calcitriol (0.25-1.0 μg/day) were promptly established. The
levels of iPTH were measured at 24 hours, at 7 and 30 days. Protracted hypoparathyroidism was considered as a subnormal iPTH concentration (less than 13 mg/dL) with necessity for calcium replacement for at least 4-6 weeks after thyroidectomy. This condition was defined persistent when lasted for more than 1 year. Plasma concentrations of 25-hydroxyvitamin D were not determined before surgery, and after operation only in patients with protracted hypoparathyroidism.

Statistics

Statistical analysis was performed using SPSS (IBM corporation, NY, USA) 18.0. Results were considered significant for p<0.05. Due to the non-normal distribution of some variables and the relatively small sample size, the non-parametric tests were cautiously used and data were expressed in median and interquartile range values. As preliminary step the interdependence between the principal clinical variables was evaluated in each group by univariate analysis. Intragroup comparison with baseline values was performed with the Wilcoxon test. Intergroup (NTP Vs control) comparison was performed at timed intervals with the two-fold Mann-Whitney test for the continuous variables and with the Pearson’s Chi-square for the dichotomic ones, respectively.

Results

We were able to carry out NTP according to the foreseen technique in nearly all 50 patients. In one instance only the NTP was not feasible because major and involuntary manipulation of the parathyroid gland. In this single case the damaged gland was implanted in the sternocleidomastoid muscle. Propensity score selected a group of 23 patients/group for matching. The two groups resulted homogeneous for all pairing criteria, as summarized in Table I. All outcomes variables were illustrated in Table II. Operative times were comparable between groups whereas both, intra and postoperative blood loss were significantly less abundant in the NTP group. No mortality has been observed in either group. Furthermore, no laryngeal permanent paralysis was experienced. Hospital stay was shorter yet not significantly in NTP group. Neither hypocalcemic crisis nor permanent hypoparathyroidism were described in either group.

The evolution of parathyroid function markers is summarized in Fig. 2. Interestingly, at day1 median (interquartile range) serum calcium levels (NTP Vs control) were 9.00 (8.20-9.65) mg/dL vs 8.50 (7.40-8.90) mg/dL (p=0.03) and at day 2, 8.70 (8.20-9.20) mg/dL vs 8.05 (7.30-8.50) mg/dL (p=0.002), respectively. Afterwards the difference between group persisted up to 2 months from the procedure. The trend of the serum levels of iPTH confirmed that NTP group received minimal damage of the parathyroid gland during the procedure compared to the control group (Table II). At day 1 iPTH median (interquartile range) dosages were 34.1 (26.6-43.9) mg/dL vs 25.4 (17.0-35.4) mg/dL (p=0.004) and at day 7, 33.0 (25.0-43.5) mg/dL vs 22.4 (16.4-30.1) mg/dL, (p=0.001), respectively.

Discussion

Total thyroidectomy can be now performed safely because of technical improvements and better knowledge of thyroid anatomy. However, parathyroid damage with postoperative hypocalcemia can still occur even in experienced hands. Furthermore, parathyroid insufficiency is somewhat problematic and difficult to treat. Preservation of parathyroid glands and maintaining their blood supply during the thyroid surgery is then of paramount importance. Hypocalcemia may arise after inadvertent removal of parathyroid glands in surgery, devascularization of glands, hyperthermic energy delivery and
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Direct trauma to parathyroid glands \(^{24-26}\). However, just simple manipulation of the gland with forceps, or traction, contusion and electro-conduction, especially if accomplished in the proximity of the vascular pole, can lead to a significant impairment of the gland function \(^{23,27}\). The idea of performing the NTP thyroidectomy derived by a mature endocrinologist (AM) from our hospital that challenged us to dissect the glands without touching them. This time we have picked up the gauntlet. After a preliminary study on the cadaver we started the first operation in vivo. The results of this study on the role of NTP shows significant advantages in preserving the integrity and functionality of parathyroid glands. The technical background of NTP it is not only the "gentle handling" of the parathyroid glands, but only if the glands are not directly or indirectly touched, compressed, and minimally devascularized, their optimal functioning is guaranteed.

Our technique figures an initial dissection from the anti-vascular pole with the research of the cleavage plan from the thyroid gland. Whenever this surgical path is absent the dissection can become sharp separating the thyroid from the parathyroid gland by leaving with a negligible amount of thyroid tissue around them (Fig. 1).

From the analysis of our pilot study we observed that NTP technique is feasible in the nearly totality of the instances predicted as practicable. The NTP thyroidectomy presented a similar operative length of the conventional procedures despite the caution in the dissection. Interestingly, the loss of blood both during the procedure and in the postoperative period were significant reduced compared to control group. As expected hospital stay was shorter in NTP. The technique was also quite effective in preserving the parathyroid glands. We did not experience postoperative hypocalcemic crisis in the NTP group and, namely, the postoperative fall of iPTH was negligible in this group whereas a significant decrement was observed in the control group.

The idea of preserving the parathyroid glands is not recent. In the past staining agents such as methylene blue \(^{28,29}\) or 5-aminolevulinic acid (5-ALA) \(^{30,31}\) have been used to individuate parathyroid glands during thyroidectomy but adverse effects have been reported. Intravenous administration of methylene blue showed a staining rate of approximately 100% but only for the localization of enlarged glands. However normal parathyroid glands can be confused with stained lymph nodes and thyroid tissue \(^{29}\).

At present, intraoperative sestamibi scintigraphy using a gamma probe is the most established in localizing enlarged parathyroid glands, especially in ectopic sites\(^{32}\). Intraoperatively, parathyroid glands would show red fluorescence under the blue light with a wavelength of 380-440 nm after the administration of 5-aminolevulinic acid, which converted into protoporphyrin IX. However, the technique may be uncomfortable because patients should be protected from direct light exposure within 48 hours postoperatively.

Optical coherence tomography (OCT) imaging has recently shown promising capability to discriminate...
parathyroid tissue from other tissues in the operating field. Miniaturization of OCT technique with the development of sterile intraoperative probe might reveal an effective way to provide an intraoperative “optical biopsy.” Recently, particles of carbon nanoparticles have been successfully used to better evidence parathyroid. Results are promising but they look expensive and time-consuming.

Limitation
This is a retrospective study performed in a limited sample size of patients, whereas propensity score 1:1 (NTP Vs control) matching allows us to be more confident about results.

Conclusions
We conclude that NTP thyroidectomy is a feasible technique in a vast majority of the instances. With respect to the traditional technique, NTP allowed a significant reduction of blood loss both intra and postoperatively. The technique did not prolong the operative time, whereas reduced, yet not significantly, the hospital stay. The group who underwent NTP thyroidectomy showed stable postoperative values of calcium and iPTH with no hypocalcemic crisis. All these features make NTP feasible, safe and worthy to be applied on routine basis. Surgery is science of cleavage plans: this method can be assumed as a typical surgical trick.

Riassunto
L’ipocalcemia è una complicanza severa dopo tiroidectomia. Al fine di preservare l’integrità delle paratiroidi senza influenzare la durata della procedura, abbiamo sviluppato un semplice metodo, caratterizzato dalla riduzione della manipolazione intraoperatoria delle ghiandole, una volta individuate. Il metodo è stato denominato “no-touch paratiroidec (NTP).” Abbiamo eseguito tiroidectomie totali extracapsulari con la tecnica NTP in 50 casi consecutivi di gozzo benigno, tra luglio 2014 e giugno 2015. Le paratiroidi sono state identificate evitando manipolazioni o traumi e preservando la loro vascolarizzazione. Per la dissezione dei nervi laringei. La degenza ospedaliera è stata più breve, ma non in modo significativo, nel gruppo NTP. In entrambi i gruppi non sono state descritte ne crisi di ipocalcemia, ne ipoparatiroidismo permanente. I livelli sierici di calcio (NTP VS controllo) erano significativamente più alti nel gruppo NTP al giorno 1 (p = 0,03) ed al giorno 2 (p = 0,002). I dosaggi di paratormone intatto sono stati significativamente più elevati al giorno 1 (p = 0,004) e il giorno 7 (p = 0,001). Conclusioni: La tiroidectomia con NTP è realizzabile nella maggior parte dei pazienti, consentendo una significativa riduzione della perdita di sangue senza prolungamento dei tempi operatori. Dopo la procedura, entrambi i valori di calcemia e paratormone intatto sono stati stabili e non è stata evidenziata nessuna crisi di ipocalcemia.

References


La tecnica per evitare ogni possibile danno alle paratiroidi in corso di eseresi lobare o totale della tiroide è sempre primariamente mirata a preservarle la vascolarizzazione, e dunque l’approccio centrifugo dalla capsula triroidia seguito nel presente studio è appunto quello più in grado di raggiungere lo scopo. Un solo suggerimento è utile da seguire: è opportuno allacciare e sezionare la vena triroidia media soltanto dopo aver sezionato – separatamente – i tre rami di divisione dell’arteria triroidia superiore per evitare che una eccessiva stasi venosa faccia aumentare di volume il lobo tiroideo ed evitando così la possibilità di sanguinamento di ogni piccolo vaso della superficie capsulare, rendendo meno chiaro il campo operatorio ed allungando i tempi dell’intervento.

A tale scopo il taglio cervicale alto secondo Crile, sulla plica cutanea sempre presente e in genere non più ampio di 7-8 cm, è quello più adatto a poter raggiungere meglio il polo superiore della tiroide dopo aver distaccato l’insezione mediale superiore di almeno parte dei muscoli nastriformi, e quindi procedere alla preparazione del polo vascolare superiore. Si procede quindi all’isolamento progressivo e quindi sezione tra lacci dei tre rami di divisione dell’arteria triroidia superiore. L’uso di due lacci prossimali, di cui il primo funge addirittura da divaricatore per applicare un secondo più prossimale, e poi un terzo a stretto contatto della capsula triroidia, garantisce un’emostasi senza possibilità di caduta dei lacci ed una liberazione totalmente esangue del polo superiore. Solo dopo questa fase è consigliabile procedere alla allacciatura e sezionatura della vena triroidia media per liberare il lato esterno del lobo tiroideo e procedere all’identificazione del nervo laringeo inferiore.

The technique to avoid any possible damage to the parathyroids performing a lobectomy or total extracapsular thyroidectomy is always primarily aimed in preserving their vascularization, and therefore the centrifugal approach from the thyroid capsule, described in the present study is exactly the better to be able in achieving the purpose. A useful suggestion to follow is to delay the severing of the middle thyroidal vein only after complete devascularisation of the upper pole of the lobe to prevent excessive venous stasis responsible of an increasing volume of the thyroid lobe and enhancing the possibility of bleeding of each small venule from the capsular surface, making less clear the operative field and lengthening the time of surgery.

To do this, the high cervical incision according Crile, on the always existing skinfold, typically no wider than 7-8 cm, it is the right one for better reaching the upper pole of the thyroid gland after detaching at least the medial superior insertion of the ribbon-like muscles, and then proceeding in the preparation of the upper vascular pole. Then one have to proceed with the progressive isolation-section between laces of the three branches of the upper thyroid artery division. The use of two proximal laces, the first of which acts even by a downward retractor to apply a second more proximally, and then a third closely the thyroid capsule, ensures efficacious hemostasis without the possibility of falling of the laces and a totally bloodless liberation of the upper pole. Only after this steps it is advisable to lacing and section of the middle thyroid vein to free the outer side of the thyroid lobe and proceed to the identification of the inferior laryngeal nerve.

**Commento e Commentary**

**Prof. Nicola Picardi**  
Ordinario di Chirurgia Generale

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