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**Study Name:** Comparison Of The Incidence Of Recurrent Laryngeal Injury Following The Dissection Of The Nerve By Cranio-Caudal And Lateral Approach By Using Introperative Nerve Monitoring

**Study Design:** This prospective study was approved by the institutional review board and informed consent was obtained from each patient. A total of 327 patients who were referred to undergo thyroid surgery between June 2018 and November 2019 were assessed for the eligibility to participate in the study. Of these, 233 were considered to be eligible for the study. Exclusion criteria included previous thyroid or parathyroid surgery, substernal goiter, preoperative VCP, evidence of lateral lymph node metastasis, intentional transection of the RLN due to tumor invasion, failure to assess RLN functioning due to equipment issues with the IONM setup, presurgical dissection amplitude of <500μV and patient’s refusal to participate in the study. Of 327 patients, 94 were excluded preoperatively due to previous neck surgery (n=47), evidence of lateral neck metastasis(n=24), patient’s refusal (n=13) and presence of substernal goiter (n=10). The remaining 233 patients were randomized to have RLN’s identified by lateral (n=121) or cranio-caudal approach (n=112 (Figure 1). Computer generated random numbers were generated and printed on cards. These cards were placed in sealed, opaque envelopes. On the morning of operation, one envelope was opened before the operation and, depending of the parity of the number, RLN’s of the patient were dissected either by cranio-caudal or lateral dissection during the operation. The patients and the nerves at risk (NAR’s) in the lateral and cranio-caudal approach groups were classified as group 1 and 2, respectively. In group 1 and 2, nine and twenty-six patients were further excluded, respectively, owing to intraoperative failure to assess RLN functioning due to equipment issues with the IONM setup or presurgical dissection amplitude of <500μV.

Thus, the data of 198 patients were analysed for primary and secondary outcome measures. The primary endpoint was RLN injury and the secondary endpoints included the effect of clinicopathological features, anatomic variations and adverse EMG changes on the occurrence of RLN injury. Of 198 patients, 112 were in the lateral approach group (group 1) and 86 in the cranio-caudal approach group (group 2). Total thyroidectomy or lobectomy was
performed in 158 (79.8%) and 40 (20.2%) patients, respectively. Sixteen (8%) patients underwent unilateral central lymph node dissection (CLND) additional to total thyroidectomy. Age, gender, body mass index (BMI), the indications for surgery, presence of hyperthyroidism, evidence of autoimmune thyroid disease (ATD) and thyroid lobe volume were recorded in all patients, preoperatively. Thyroid lobe volume was calculated by using the dimensions (length(L), width(W), thickness(T)) of each thyroid lobe measured by ultrasonography according to the following formula; \( \frac{\pi}{6} \times L \times W \times T \).

All NAR’s were dissected by using CIONM including vagal response evaluation at the beginning and at the end of the operation (IONM = L1, V1, R1, R2, V2, L2) according to the recommendations by the International Intraoperative Neural Monitoring Study Group. All patients underwent pre-, and postoperative laryngoscopic examination within 2 days after surgery, and repeated serially if abnormal (L1, L2). All operations were performed by experienced endocrine surgeons. Length of RLN dissection was defined as extended if it the nerve was dissected for 5 cm or greater. Duration of lobectomy for each site, period of time for initial identification of RLN after the mobilization of upper pole on each site, the relationship of the RLN to the ligament of Berry (LOB) and to the Tubercle of Zukerkandl (TZ) (if present), extralaryngeal branching of the RLN, length of RLN dissection, presurgery and postsurgery amplitude and latency of the vagus and the RLN, occurrence of adverse EMG changes and recovery time or loss of signal (LOS) were recorded intraoperatively in all patients. Serum levels of calcium and parathormone on the first postoperative day were analyzed in all patients. The rates of post-thyroidectomy hypoparathyroidism and vocal cord palsy (VCP) were recorded. Final histopathological diagnosis was documented in all patients, postoperatively.

Demographic data, BMI, the indications for surgery, clinicopathological features, thyroid volume, duration of the operation, period of time for RLN identification, anatomical variations, length of RLN dissection, presurgery and postsurgery amplitude and latency of the vagus and RLN, the rate of adverse EMG changes, LOS and morbidity (vocal cord palsy, hypoparathyroidism) were compared between group 1 and 2. The correlation between intraoperative adverse EMG changes and anatomic variations, lobe volume and type of thyroid disease was investigated as well.

Thyroid surgery and CIONM technique
All operations were performed under general anesthesia by using a small dose (0.3 mg/kg) of non-depolarizing muscle relaxant (Esmeron; MSD Sharp &Dohme GmbH, Haar, Germany) at intubation. The endotracheal tube was properly inserted to ensure that the recording surface electrode was placed at the level of the vocal cords. Prior to lobectomy, the carotid sheath was carefully dissected and the vagus nerve was identified using a hand held stimulation probe. The vagus nerve was dissected over a distance of ≤ 1 cm to place the vagus electrode. (automated periodic stimulation (APS) (Medtronic Xomed, Jacksonville,FL) or saxaphone probe (vagus electrode) (Dr.Langer Medical GmbH, Avalanche SI, Germany).

The baselines for latency and amplitude were automatically calibrated after the connection of the vagus electrode with the neuromonitoring system. CIONM had been carried out with one of the two following commercially available neuromonitoring devices: (1)NIM 3.0 Nerve Monitoring Systems; Medtronic Xomed, Jacksonville,FL; or (2) Dr. Langer Medical GmbH, Avalanche SI, Germany. Achievement of initial presurgical dissection amplitude of ≥500µV was aimed in all patients. During the operations, adverse EMG parameters were defined as amplitude decrease of 50% or more of baseline value and, or latency increase of 10% or more. A combined event (CE) was defined as concordant amplitude decrease of more than 50% and latency increase of more than 10%, regarding to baseline values. The surgical maneuver was immediately altered and the traction released if adverse EMG changes were noted during surgery and waited to achieve the recovery of EMG changes. Recovery was defined as amplitude recovery to >50% of the initial baseline amplitude. Loss of signal (LOS) was defined as amplitude <100µV. In case of LOS during the surgery of initial site, contralateral surgery was aborted if the amplitude did not recover to greater than 50% of the initial baseline amplitude within 20 minutes of the initial decline. During surgery, isthmus was divided first in both group of patients. Then the upper lobe of the gland was dissected through the avascular zone between the upper lobe and the cricothyroid muscle. The external branch of the superior laryngeal nerve was identified visually and, or by using neuro-monitoring hand probe prior to dissection of the upper pole vessels, and then the branches of upper pole vessels were ligated individually. Identification and preservation of all parathyroid glands and their vascular supply was tried in all cases. In case of incidental parathyroidectomy or totally compromised vascularity of the parathyroid glands, autotransplantation in to sternocleidomastoid muscle was performed.

**RLN identification**
**Lateral approach:** Following the ligation of upper pole vessels, the thyroid lobe was pulled anteromedially and the RLN was sought within the carotid triangle at the level of inferior thyroid artery (ITA). The tissue between the carotid artery and the trachea was dissected gently parallel to the direction of the nerve until the nerve is identified visually and by hand held stimulation probe. After the identification of RLN, the vessels of inferior thyroid lobe was ligated. The nerve was dissected along its course to the entry point, and then the thyroid lobe was totally dissected from the trachea and the lobectomy was completed. If adverse EMG changes were encountered during lateral approach, traction was released immediately and waited for recovery. If the adverse EMG changes recovered, RLN dissection was proceeded by lateral approach again. If the adverse EMG changes did not recover after traction release or in case of repeated adverse EMG changes, lateral approach was abandoned. The thyroid lobe was retracted laterally and medial aspect of the lobe was dissected from the trachea. The RLN dissection was continued by medial approach in such cases.

**Cranio-caudal approach:** Following the ligation of upper pole vessels, the upper pole was retracted antero-medially to expose crico-pharyngeal muscle. The RLN was identified at the point of entry both visually and with hand held stimulation probe. The RLN dissection was proceeded craniocaudally by the division of the suspensory ligaments of the LOB through the level of ITA. After the identification and visualization of the RLN through its whole course, the medial and inferior vessels of the thyroid gland were dissected and ligated. Then, the lobe was dissected from the trachea and lobectomy was completed. If adverse EMG changes were encountered during cranio-caudal approach, traction was released immediately and waited for recovery. The RLN dissection was proceeded by cranio-caudal fashion again if the EMG changes recovered. If the EMG changes did not recover or in case of repeated adverse EMG changes, cranio-caudal approach was abandoned and RLN was dissected by lateral approach. If repeated adverse EMG changes were encountered despite conversion from cranio-caudal to lateral approach, then the lobe was retracted laterally and medial aspect of the lobe was dissected from the trachea. The RLN was dissected by medial approach in such cases with repeated adverse EMG changes.