USE OF INTRAOPERATIVE NEURAL MONITORING FOR PROGNOSTICATION OF RECOVERY OF VOCAL MOBILITY AND REDUCTION OF PERMANENT VOCAL PARALYSIS AFTER THYROIDECTOMY

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Funding: None

Running Title: Neural monitoring and permanent vocal palsy after thyroidectomy

Key words: Thyroidectomy; vocal palsy; neural monitoring; recurrent laryngeal nerve; branching

ABSTRACT

INTRODUCTION

The benefits of intraoperative neural monitoring (IONM) of recurrent laryngeal nerve (RLN) on post-thyroidectomy vocal cord palsy (VCP) rates are contentious. We wished to study impact of IONM on permanent VCP after thyroidectomy.

METHODS

Retrospective review of prospective series of 1011 (1539 nerves-at-risk) patients undergoing thyroidectomy without (418, Group 1) and with (583, Group 2) IONM.

RESULTS

There were 3 recognized nerve injuries in Group 1, versus 1 in Group 2 (p=0.3). There were no differences in overall VCP rates. However, patients in Group 2 with immediate postoperative VCP had higher likelihood of full recovery than patients in Group 1 (55/56 versus 23/29, p=0.01), and lower incidence of total permanent VCP (2/917 versus 9/647, p=0.01).

CONCLUSION

Among patients with immediate postoperative VCP after thyroidectomy, IONM is associated with a higher likelihood of regaining normal vocal function. This may be related to better identification of RLN branching in IONM cases.

INTRODUCTION

Damage to recurrent laryngeal nerve (RLN) leading to vocal cord palsy (VCP) and consequent dysphonia is one of the most significant complications of thyroidectomy, and may lead to patient distress, adverse impact on quality of life, and reduced earning potential[1]. Transient VCP (resolving within 6 months) is thought to occur due to stretching, thermal injury, or compression to the RLN, which leads to neuropraxic injury to the RLN, and consequent vocal ford paresis or paralysis[2]. Permanent VCP (persisting beyond 6 months) arises from more severe RLN injury, most commonly nerve section, but possibly also by more severe degrees of stretching or thermal injury, resulting in axontomesis or neurotmesis, leading to synkinesis, incomplete, or no recovery of vocal cord function. However, reasons for failure of some anatomically preserved RLNs to regain full functionality remain unclear.

Visual identification of the RLN during thyroidectomy is considered gold standard in order to minimize the risk of inadvertent RLN damage[3]. Recently, there has been increasing usage of RLN monitoring devices. Most of these incorporate a stimulating probe which is used to intermittently stimulate the putative RLN, eliciting a response which is detected by a laryngeal electrode attached to the endotracheal tube. In theory, this should reduce the risk of inadvertent neural injury, by allowing "testing" of structures prior to division, and thus reduce the risk of unwitting division of the RLN[4-11]. However, published literature regarding the efficacy of RLN monitors in reducing the incidence of post thyroidectomy VCP is conflicting[12-19].

The purpose of the present paper was to study vocal outcomes after thyroidectomy, and, in particular, to study factors which may prognosticate for recovery of vocal function and long-term vocal outcomes. The senior author of the present paper (PS) has prospectively collected data on all thyroid surgeries and vocal cord outcomes for over a decade. During this period, surgical details, intraoperative events, and immediate and long-term vocal outcomes have been consistently and meticulously documented. In addition, during the period covered by this review, the RLN monitor was introduced into our practice. This afforded an opportunity to study the impact of RLN monitoring on rates of VCP, recovery of vocal mobility, and long-term vocal function.

METHODS

This study was approved by the Cork Clinical Research Ethics Committee and the Data Protection Office in the South Infirmary Victoria University Hospital. The study comprised a retrospective review of a prospectively maintained database of all thyroid operations performed by the senior author (PS) over a 10-year period between March 2009 and June 2019, inclusive. In the early part of this series, operations were performed without use of IONM. RLN monitoring equipment was purchased by the hospital in October 2013 and used as standard for thyroidectomy cases after that. Between October 2013 and January 2016, the Neurosign 100 nerve monitor (Magstim Company Ltd, UK), with lantern laryngeal electrodes were used. From 2016 onwards, Medtronic NIM Nerve monitoring system 3.0 (Medtronic, Ireland) with NIM Trivantage EMG endotracheal tubes were used. In nearly all cases, intermittent nerve monitoring was employed. A small number of cases towards the latter end of the series were monitored by automated period stimulation (APS) of vagus nerve, and were excluded from the present study.

Inclusion criteria for the present study were all thyroid operations performed during the study period. Exclusion criteria were cases with pre-existing VCP on the side ipsilateral to that undergoing surgery, RLNs undergoing deliberate sacrifice due to cancer, cases without postoperative vocal cord check, cases of thyroid isthmusectomy without RLN dissection, and cases undergoing APS monitoring. Among patients with pre-existing VCP or undergoing RLN sacrifice, the contralateral RLN was included if bilateral thyroidectomy had been performed.

The surgical technique varied according to the particulars of the case. In nearly all cases, total removal of all visible thyroid tissue on the side undergoing surgery was performed. In general, we performed initial mobilization of the upper pole, followed by the lower pole, with ligation of inferior thyroid veins, and capsular dissection of the thyroid and reflection of parathyroids and parathyroid containing tissue off the thyroid gland, at all times watching out for the possibility of a RLN adherent to the lower thyroid and being tented out of the wound on lower pole elevation. Once mobilization of both upper and lower poles of thyroid was completed, attempts were made to locate the RLN, around the tubercle of Zuckerkandl (Singh's pointer), close to its entry point into the larynx. We aimed to definitively identify the RLN in all cases. In cases where IONM was used, this was used to confirm the RLN, as well as to test branches of inferior thyroid artery in the region of Berry's ligament, prior to ligation of same. An intact response from the most proximally exposed part of the RLN was considered to constitute an intact pathway. We did not routinely expose or stimulate the vagus nerve in IONM cases.

Our policy was for all patients undergoing thyroidectomy to undergo both preoperative and postoperative laryngoscopy. For the first few years of the study period, largely coinciding with the period where IONM was not used, postoperative laryngoscopy was performed at the out-patient clinic, 2-4 weeks postop. From ca. 2013 onwards, this switched to laryngoscopy being routinely performed on the morning after surgery, prior to discharge from hospital. For the purpose of the study, we considered any absent or reduced movement of vocal fold to constitute VCP. We did not attempt to differentiate between partial or complete palsy due to the subjectivity in determining this in many cases. Patients with VCP were generally followed up at 3-6 weeks, 3-4 months, and 6 months postoperatively. Any persistent VCP or reduced vocal movement at 6 months was considered permanent.

Data recorded in the database and extracted for the purpose of the present study included: age, sex, indication for surgery; extent of surgery; intraoperative findings (including thyroid retrosternal extension, findings of branched or bifurcating RLN, and subjective finding of RLN densely stuck to adhesions, tumour, or thyroid capsule); intraoperative events (including difficulties with RLN identification, inadvertent RLN transection, and loss of signal or other difficulties with nerve monitor in cases undergoing IONM); final diagnosis; and postoperative voice and vocal mobility. For the purposes of the study: revision surgery was considered to have been performed where thyroidectomy was performed on the same side as previously dissected. Thus, "completion" thyroidectomies, comprising removal of remaining thyroid tissue contralateral to the previously dissected side, were not included in revision cases. Similarly, where completion thyroidectomy was performed due to cancer diagnosis in the initially resected lobe, these cases were not included with cancer diagnosis. Pretracheal lymph node dissections without dissection of either RLN were excluded from central neck dissection (CND).

Statistical analysis was performed using XLSTAT 2015.1.03 (Addinsoft, France, 2015). Statistical analysis of impact of factors on risk of VCP was performed on a per-nerve-at-risk basis, with denominator being number of nerves-at-risk in relevant group. A Fisher's exact test was used on 2x2 contingency tables. Multivariate analysis of predictors of any postoperative VCP was performed using logistic regression analysis. Due to small number of events, multivariate analysis was not performed in the case of permanent vovcal cord palsy.

RESULTS

Study population:

During the study period, 1031 patients underwent thyroid surgery. Thirty patients were excluded due to having undergone isthmusectomy only (7); pre-existing VCP (5); use of APS (10), refusal of postoperative laryngoscopy (7, 4 undergoing IONM), and deliberate sacrifice of RLN due to encasement by medullary carcinoma in patient undergoing unilateral surgery (1). All 7 patients refusing postoperative laryngoscopy had normal voice postoperatively, and all 4 of those undergoing IONM had intact neural responses at the end of the case. Nine further patients undergoing bilateral surgery had one NAR excluded. Eight (3 with pre-existing VCP) with thyroid cancer underwent deliberate sacrifice of unilateral involved RLN, and one undergoing excision of a paraganglioma involving the thyroid lobe and carotid sheath underwent inadvertent resection of vagus nerve. Among cases undergoing RLN sacrifice, 6 (3 undergoing IONM) had complete neural encasement by tumour, while in 2 (1 undergoing IONM) initial efforts to separate the nerve from cancer were unsuccessful, followed by more hazardous “last-ditch” manoeuvres to approach the nerve from above, resulting in transection of the nerve at its entry point into the larynx. The case undergoing paraganglionoma resection was performed using IONM; in this case the RLN had been preserved, evidenced by intact response to stimulation of proximal RLN after medial to lateral release of thyroid off trachea, but ended up with proximal resection of vagus nerve, and so was excluded from the study. . The final study population thus consisted of 1001 patients, of whom 418 (647 NARs) underwent surgery without IONM (group 1), and 583 (892 NARs) with IOMN (group 2). Among patients in Group 2, type of IONM used was Neurosign in 261 cases, and NIM in 322 cases. The clinical and demographic features of these patients according to use of IONM is given in Table 1. There were significantly more males (p=0.01) and patients with Graves disease (p=0.0001) undergoing surgery in the latter period of the study with use of IONM.

Intraoperative findings

Twenty six patients had grossly invasive cancer, (9 in Group 1, 17 in Group 2, p=0.55). Excluding 8 hemithyroids where RLN was deliberately sacrificed, grossly invasive cancer was present on the same side as 21 NARs included in the study (5 group 1, 16 group 2, p=0.12). This was involving the RLN, which was preserved, in 9 cases (3 group 1, 5 group 2, p>0.99). Invasion of RLN was by the primary thyroid cancer in 8 cases, and by metastatic nodes in 1 case.

In 55 cases in Group 1, and 64 cases in Group 2, the RLN was recorded as having been densely adherent to adhesions, tumour, or thyroid capsule (p=0.34).

Branching of RLN was recognized in 85 cases in Group 1, and 163 cases in Group 2. The difference was significant (p=0.008). Only 1 right-sided non-recurrent RLN was identified in Group 1.

Intraoperative events

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There were 4 cases of recognized inadvertent intraoperative RLN section, 3 in Group 1 (0.5%), and 1 in Group 2 (0.1%). The difference was not significant (p=0.3).

Among Group 2, there were 58 cases of loss of or absent neuromonitoring signal (23 temporary, 35 permanent). Based on loss of signal (LOS), 3 patients who were planned for total thyroidectomy only underwent unilateral lobectomy on the day. In addition, in 24 cases the nerve monitor did not work. Most (23) of these were cases where the Neurosign nerve monitor with lantern electrode had been used.

Postoperative vocal cord function according to IONM

All 4 cases with inadvertent RLN section had postoperative complete VCP. Among NAR where the RLN was preserved, postoperative impaired mobility was present in 85 (5.5%) (30 in Group 1, and 55 in Group 2, p=0.21). This was noted to be partial in 36 cases (2.3%), and complete in 49 cases (3.2%). Complete follow-up was available for 84/85 patients. Full recovery was seen in 77/84 cases (91.7%), with a mean time to full recovery of 10.9 weeks. One patient in Group 1 whose voice returned to normal refused further laryngoscopy.Recovery of vocal function was seen more frequently in Group 2. In Group 1 (no IONM), there were 6 cases of RLN considered to have been preserved intact, but never regained normal mobility. Two of these cases did regain partial mobility, but had persistent reduced mobility at 6 months, with persistent minor vocal symptoms (fatiguing). In 1/6 cases, the RLN had not been identified with confidence. In all others, surgery had proceeded uneventfully with identification and preservation of the RLN and the postoperative VCP had been an unexpected finding. The incidence of full recovery of vocal mobility among cases in Group 1 where the RLN was considered to have been preserved intact was 79% (23/29).

In contrast, in Group 2 (with IONM), full recovery of vocal function was seen in 54 of 55 nerves (98.2%), which was significantly higher than Group 1 (p=0.01). Notably, the single case without recovery involved a case where the RLN was densely adherent to a 4.5cm length of tumour which was also invading through-and-through into the trachea. Therefore, despite preservation of the RLN in this case, an absent, or in very protracted, recovery of vocal function may have been anticipated.

There was a significant difference between the groups in incidence of total permanent VCP (including recognized intraoperative nerve injury and non-recovering nerves). In Group 1 (without IONM), the rate of permanent VCP was 1.4% (9/647), versus 0.2% (2/892) in Group 2 (p=0.01) (Table 2).

Vocal mobility within IONM group according to neuromonitoring events

Postoperative VCP was present 29/35 patients in Group 2 with absent signal or permanent LOS, and 6/23 patients with TLOS. Among 55 patients with postoperative VCP, 35 had intraoperative permanent or temporary LOS. In a further 7 cases, note was made of requirement for higher stimulation or lower output, while in 3 cases, the IONM was noted as not functioning. In 10 cases, neural signal was recorded as normal. Of these, 7 had postoperative reduced but intact vocal movement, and 3 had vocal palsy. 6 patients had normal voice, 2 were slightly hoarse, and 2 had breathy voice.

Other factors impacting postoperative vocal mobility

Risk factors for any postoperative vocal palsy are shown in Table 3. Significant factors on univariate analysis were revision surgery (p=0.02), cancer diagnosis (p=0.01), invasive cancer (p<0.0001), branching RLN (p=0.005), and RLN "stuck" to adhesions, tumour, or thyroid capsule (p<0.0001).

On multivariate analysis, factors remaining significant were revision surgery (OR 3.3, 95% CI 2.0, 9.0, p=0.02), invasive cancer (OR=12.3, 95% CI 4.2, 36.5, p<0.0001), branching RLN (OR 1.7, 95% CI 1.1, 3.0, p=0.03), and RLN "stuck" to adhesions, tumour, or thyroid capsule (OR 2.2, 95% CI 1.2, 4.1, p=0.01).

Risk factors for permanent VCP are also shown in Table 3. Significant risk factors were revision surgery (p=0.002), retrosternal goiter (p=0.005), and no use of IONM (p=0.02). Because there were <20 events, we did not perform multivariate analysis.

DISCUSSION

Despite the increasingly widespread use of nerve monitoring systems in thyroid surgery, evidence to support an impact of IONM on postoperative VCP rates is contentious. One of the major challenges in studying the impact of nerve monitoring on vocal outcomes in thyroidectomy is the already low incidence of VCP among high volume surgeons even without nerve monitoring. Much of the recently published literature on IONM in thyroidectomy is based on large database studies[12-14,20] or meta-analyses[6-8,16-18,21,22]. These studies have the advantage of including very large case numbers, so being adequately powered to detect small differences. However, these studies can suffer from shortcomings of variability in patient cohorts, indications for surgery, institution and surgeon volumes, surgical techniques, and, in the case of database studies, incompleteness of data entry, inability to differentiate between transient and permanent VCP[12,14,20], incompleteness of follow up data where this is available[13], and under-reporting of complications[23]. Single institution studies, like the present one, have the advantage of consistency in all of the above, but may be underpowered to detect significant differences. In addition, the findings from any single institution study may not be automatically extrapolatable to other units with different patient cohorts, surgical techniques, and levels of surgical experience.

The major finding from the present study was a reduction in the incidence of permanent VCP with use of IONM. This appears to be mainly related to a significant benefit of IONM in prognosticating recovery of vocal mobility after thyroidectomy. That is, among those cases where the RLN is identified and preserved, but which develop postoperative VCP, vocal mobility is significantly more likely to return to normal where IONM has been used. In contrast, there appears to be a significantly higher incidence of vocal folds not regaining full mobility in the non-monitored group.

One possible reason for the better prognostication and lower rate of permanent VCP in the IONM group was enhanced ability to recognize branching of the RLN. It is possible that the higher rate of long term impaired vocal mobility in the non-IONM group, in cases where it was considered that the

RLN had been preserved, may have been due to unrecognized division of an anterior branch of the RLN. The anterior branch of the RLN carries the major supply to the adductor muscles of the vocal cord[24,25], and so unrecognized division of this could lead to permanent VCP despite apparent intact RLN. Consistent with this theory is that in this series, we were significantly more likely to recognize branching of the RLN in cases undergoing IONM, and during the course of IONM cases, we liberally utilized neural stimulation to test putative blood vessels in the vicinity of the RLN prior to ligation. Interestingly, in other prospective studies, Barczynski et al, and Anuwong et al, also reported more branched RLNs in the group undergoing IONM[4,26].

Another possible reason for superior recovery of RLNs with postoperative VCP in the IONM group was a change in operative strategy in cases where there was loss of signal intraoperatively. In such cases, great efforts were always made for the rest of the case to absolutely minimize any more stretching of the RLN. It is conceivable that this may have limited the degree of axonal injury, which facilitated full recovery, in contrast to cases performed without IONM where such manoeuvres may have been unwittingly continued for the rest of the case, leading to more severe degree of axonal injury and incomplete or no long-term recovery. This theory forms much of the rationale for continuous IONM. Continuous IONM with APS of the vagus nerve may alert the surgeon to impending neural injury, and facilitate modification of surgical manoeuvres which reduce traction on the RLN, and may allow for further reduction in transient and permanent VCP rates[26-30]. However, continuous IONM is not yet widespread, and further data demonstrating conclusive additional benefit over intermittent IONM is awaited. In the present study, we excluded the small number of APS cases performed in our unit, in order to ensure a homogenous cohort within the IONM group.

Among other authors, Vasileiadis et al also found a significant improvement in permanent VCP rates in favour IONM of in a larger single institution retrospective series of 2556 patients[10], while Bergenfelz at al reported a lower incidence of permanent VCP with IONM among patients registered in the Scandinavian Quality Register for Thyroid, Parathyroid and Adrenal surgery undergoing thyroidectomy with postoperative laryngoscopy[13]. Advantages of the present study over that of Vasileiadis et al include the prospective data collection and follow-up, and the more complete recording of intraoperative findings and events. It is interesting that while the overall incidence of permanent VCP was similar between our study (0.3%) and that of Vasileiadis (0.5%), the reported incidence of transient VCP was much lower in Vasileiadis' study (1.3% versus 5.5%). It is possible that this discrepancy may be due to incomplete capture of some cases of VCP with retrospective study design. Among prospective studies, Barczynski et al reported in a randomized clinical trial a lower incidence of transient and overall VCP in the nerve monitoring group, but no significant difference in permanent VCP rates[4]. Other prospective studies also found no significant differences in VCP rates according to use of nerve monitoring[9,15,31,32]. However, most of these other studies were small, while that of Mirallie et al was a multicentre study with relatively high VCP rate, possibly reflecting a heterogenous series[9]. Finally, a recently published Cochrane systematic review and meta-analysis reported no conclusive evidence of benefit for IONM over visual nerve identification alone[22]. Most of the cases in this review came from the Barczynski study, and this meta-analysis interestingly also included a study of IONM for identification of superior laryngeal nerve[33].

We did not find any difference in the incidence of temporary VCP between the groups. If anything, the incidence of transient VCP was borderline higher in patients undergoing IONM than those without. We believe that this somewhat unexpected finding is most likely explained by differences in the timing of postoperative laryngoscopy. For most patients in Group 1, this was performed at their follow-up out-patient appointment, which was usually between 2 and 4 weeks postoperatively, whereas most patients in Group 2 underwent laryngoscopy in the morning after surgery. It is thus possible we could have missed some transient neuropraxias in Group 1 that had already resolved by the time of their outpatient appointment. Consistent with this was the presence in Group 2 of 12 cases of VCP which resolved in ≤4 weeks, and 32 which resolved in ≤6 weeks. In contrast, in Group 2, only 3 cases had resolved in ≤6 weeks. The difference in timing of postoperative laryngoscopy would not have affected our findings regarding permanent VCP, however, clearly our study is not ideally designed to assess impact of IONM on incidence of transient VCP.

The major shortcoming of the study was the fact that it was non-randomized, and a valid criticism is that the improvement in VCP rates seen in the latter part of the series may have reflected increasing surgical experience rather than benefits from use of nerve monitoring. Against this, however, was the finding that among the non-monitored group, cases of permanent VCP were distributed throughout the series without any clustering in the early period (Supplementary Figure 1). Similarly, it is also possible that the description of intraoperative findings may have also evolved over time. A further issue is that we did not routinely perform vagus nerve stimulation in non-APS cases, as recommended by some international guidelines[34]. We always performed RLN stimulation at the end of dissection as proximal as possible, however, it is notable that we did have 10 cases of transient VCP in Group 2 without any evidence of LOS, which could be consistent with the site of neuropraxic injury having been proximal to the extent of dissected RLN. However, it is unlikely this would have impacted the findings of our study as we did not have any cases of unexpected permanent VCP in the IONM group. Finally, the overall low number of events of permanent VCP limits the statistical power of the study.

On the other hand, we feel our study has some major strengths. In particular, these include the prospective data collection, ensuring the complete capture of all cases of VCP and comprehensive recording of intraoperative findings and events, the high compliance with postoperative laryngoscopy, and the fastidiousness of follow-up, with all but 1 patient with immediate postoperative VCP followed until full resolution or designation as permanent VCP.

CONCLUSION

In the present study, we report a significant reduction in incidence of permanent VCP after thyroidectomy in cases undergoing IONM than those without, which seems to be largely due to greater likelihood of full recovery of vocal mobility in cases of immediate VCP where the RLN was considered to have been preserved intraoperatively in IONM cases. An important reason for this may well be avoidance of unrecognized injury to anterior RLN branches, due to better recognition of same in cases where IONM is used, a theory supported in the present series by the higher incidence of recognizing RLN branching when IONM was used. We believe the findings of the present study support a beneficial role for IONM in reducing the incidence of permanent VCP after thyroidectomy.

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	Without IONM (n=418)	With IONM (n=583)	p-value
Sex (male)	63	124	0.01
Age (mean, years)	49.4	49.7	0.61
Total thyroidectomy*	233	314	0.56
Graves disease	31	92	0.0001
Revision surgery	11	11	0.51
Retrosternal goiter	71	84	0.29
Cancer diagnosis	105	121	0.11
Grossly invasive cancer	9	17	0.55
Central neck dissection	33	34	0.20
Nerves-at-risk*	647	892	

Table 1: Clinical and demographic features of study population

* Total thyroidectomy figure includes 4 patients without IONM and 5 with IONM undergoing deliberate sacrifice of RLN or resection of vagus nerve; sacrificed nerves are excluded. Contralateral nerves are included in the Nerves-at-risk figure

	Without IONM 647 Nerves-at-risk	With IONM 892 Nerves-at-risk	
Inadvertent section	3 (0.5%)	1 (0.1%)	0.3
Immediate VCP	33 (5.1%)	56 (6.3%)	0.38
Transient VCP	24 (3.7%)	54 (6.1%)	0.04
Permanent VCP	9 (1.4%)	2 (0.2%)	0.01

Table 2: Vocal cord outcomes according to use of IONM

Variable	n	Immediate VCP (n, %)	Odds ratio	p-value	Permanent VCP (n,%)	Odds ratio	p-value
Graves disease	244	17 (7.0%)	1.27 (0.74-2.20)	0.39	3 (1.2%)	2.00 (0.53-7.60)	0.31
Revision surgery	31	5 (16.1%)	3.26 (1.22-8.70)	0.02	2 (6.5%)	11.49 (2.38-55.52)	0.002
Cancer diagnosis	380	32 (8.4%)	1.78 (1.13-2.79)	0.01	2 (0.5%)	0.68 (0.15-3.14)	0.62
Invasive cancer*	21	10 (47.6%)	16.56 (6.83-40.16)	<0.0001	1 (4.8%)	7.54 (0.92-61.73)	0.06
Central neck dissection	112	11 (9.8%)	1.88 (0.97-3.65)	0.06	1 (0.9%)	1.28 (0.16-10.06)	0.82
Retrosternal	206	16 (7.8%)	1.45 (0.83-2.55)	0.19	5 (2.4%)	5.50 (1.66-18.19)	0.005
Branching RLN	248	24 (9.7%)	2.02 (1.24-3.30)	0.005	2 (0.8%)	1.16 (0.25-5.39)	0.85

RLN “stuck”	119	18 (15.1%)	3.39 (1.94-5.90)	<0.0001	2 (1.7%)	2.68 (0.57-12.55)	0.21
IONM	892	56 (6.3%)	1.25 (0.80-1.94)	0.33	2 (0.2%)	0.16 (0.03-0.74)	0.02

Table 3: Univariate analysis of risk factors for any immediate and permanent VCP (on per-NAR basis)

* sacrificed RLNs excluded