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Laryngeal Injury and Upper Airway Symptoms after Endotracheal Intubation During Surgery: A Systematic Review and Meta-Analysis

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Abstract

Laryngeal injury from intubation can substantially impact airway, voice, and swallowing, thus necessitating multidisciplinary interventions. The goals of this systematic review were: (1) to review the types of laryngeal injuries and their patient-reported symptoms and clinical signs resulting from endotracheal intubation in patients intubated for surgeries and (2) to better understand the overall the frequency at which these injuries occur. We conducted a search of 4 online bibliographic databases (i.e., PubMed, Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and The Cochrane Library) and ProQuest and Open Access Thesis Dissertations (OPTD) from database inception to September 2019 without restrictions for language. Studies that completed post-extubation laryngeal examinations with visualization in adult patients who were endotracheally intubated for surgeries were included. We excluded: 1) retrospective studies, 2) case studies, 3) pre-existing laryngeal injury/disease, 4) patients with

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histories of or surgical interventions that risk injury to the recurrent laryngeal nerve, 5) conference abstracts, and 6) patient populations with non-focal, neurological impairments that may impact voice and swallowing function, thus making it difficult to identify isolated post-extubation laryngeal injury. Independent, double-data extraction, and risk of bias assessment followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Collaboration's criteria. Twenty-one articles (1 cross-sectional, 3 cohort, 5 case series, 12 randomized controlled trials) representing 21 surgical studies containing 6140 patients met eligibility criteria. The mean patient age across studies reporting age was 49 (95%CI: 45, 53) years with a mean intubation duration of 132 (95%CI: 106, 159) minutes. Studies reported no injuries in 80% (95%CI: 69%, 88%) of patients. All 21 studies presented on type of injury. Edema was the most frequently reported mild injury, with a prevalence of 9-84%. Vocal fold hematomas were the most frequently reported moderate injury, with a prevalence of 4% (95%CI: 2%, 10%). Severe injuries that include subluxation of the arytenoids and vocal fold paralysis are rare (<1%) outcomes. The most prevalent patient complaints post-extubation were dysphagia (43%), pain (38%), coughing (32%), a sore throat (27%), and hoarseness (27%). Overall, laryngeal injury from short-duration surgical intubation is common and is most often mild. No uniform guidelines for laryngeal assessment post-extubation from surgery are available and hoarseness is neither a good indicator of laryngeal injury or dysphagia. Protocolized screening for dysphonia and dysphagia post-extubation may lead to improved identification of injury and, therefore, improved patient outcomes and reduced healthcare utilization.

Keywords

endotracheal intubation; surgery; larynx; voice; deglutition; dysphagia; injury

INTRODUCTION

Globally, more than 320 million patients undergo surgical procedures each year.[1,2] In the United States, approximately 30% of surgeries require orotracheal intubation.[3] The placement of an endotracheal tube (ETT) for surgery is most often a planned and controlled procedure. Despite considerable skill, adequate preparation, good execution, and optimized environments, placement of an ETT may result in both short- and long-term consequences. In turn, these consequences may require additional and unplanned medical care after extubation.

Post-extubation patient complaints frequently include voice dysfunction (dysphonia), voice loss (aphonia), sore throat, and swallowing dysfunction (dysphagia).[4-7] These complaints are often dismissed or overlooked, owing to the frequent observation that they are temporary.[8] Laryngeal injuries are also believed to be minor, often going unevaluated despite the fact that more severe injuries and complications can occur.[4,6-10] As data emerge that support an association between duration of intubation and subsequent laryngeal injury,[4,11-13] it is clear that awareness of potential injury needs to extend to short-term intubation as well.

Many referrals for evaluation of laryngeal injury/voice dysfunction will occur after being present for 1 week,[14-16] even as long as 2-3 months in the setting of ongoing symptoms.[17-19]

Despite more than 100 years of intubation during surgery,[4] no standard practice for post-extubation assessment of laryngeal injury/dysphonia/dysphagia exists. Patients with laryngeal injuries are at risk for long-term functional impairment in critical laryngeal functions of voice, swallow, and airway. For example, both delayed-onset laryngeal stenosis[20,21] and chronic dysphonia[22] are reported after intubation injury.

The goals of this systematic review were: (1) to review the types of laryngeal injuries and their patient-reported symptoms and clinical signs resulting from endotracheal intubation in patients intubated for surgeries and (2) to better understand the prevalence at which these injuries and their symptoms occur. This prevalence systematic review specifically encompasses prospective studies with post-extubation laryngeal visualization.

MATERIALS AND METHODS

This systematic review on laryngeal injury post-extubation in patients after surgery followed methodology used for a separate systematic review of laryngeal injury following prolonged intubation in the intensive care unit (ICU).[11]

Literature Search

In consultation with a content expert (M.B.B.), a clinical informationist (C.P.) created the search strategy. This strategy was executed using 4 electronic bibliographic databases from their inception to April 2016: PubMed, Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Cochrane Library. Three updates (i.e., March 2017, September 2017, September 2019) were completed (Supplemental Table 1) and ProQuest, and Open Access Thesis Dissertations as part of the gray literature. Controlled vocabulary supplied by each electronic database (e.g., Medical Subject Headings, Emtree terms, and CINAHL headings) was supplemented with keywords for the broad concepts of intubation, methods of visualization, and injury. This systematic review focused on all prospective study designs that included adult humans. Pediatrics-focused research terms were excluded from titles only. Animal only research was filtered out. A research filter was applied based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE, sensitivity and precision-maximizing version[23] with additions for other types of clinical studies.

Selection Criteria

Inclusion criteria included: 1) prospective studies other than case studies, 2) adult (≥18 years old) patients who underwent scheduled surgical procedures requiring oral endotracheal intubation, 3) completed laryngoscopic evaluations using direct (e.g., line of sight) or indirect (e.g., flexible endoscopy) visualization of the larynx post-extubation, and 4) studies that reported sufficient data on laryngeal injury (e.g., frequency, nature). Exclusion criteria included: 1) retrospective studies, 2) case studies, 3) pre-existing laryngeal injury/disease, 4) patients with histories of or surgical interventions presented in the research study that risk injury to the recurrent laryngeal nerve (e.g., neck surgeries, open thoracic surgeries), 5) conference abstracts, and 6) patient populations with non-focal, neurological impairments

that may impact voice and swallowing function, making it difficult to identify isolated post-extubation laryngeal injury (e.g., stroke, Parkinson's disease).

Data Extraction/Risk of Bias Assessment

For the original search and for each update, either one of the authors (M.B.B.) or the clinical informationist (C.P.) imported the search strategy results to an online platform (Covidence: www.covidence.org, Melbourne, Victoria, Australia) for independent review. Each entry was independently screened by title, abstract, and full text by 2 authors (B.B., E.J.). Disagreements were independently resolved by a third author (M.B.B.), masked to the decision by each of the screeners. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, double-data extraction and risk of bias assessment were independently completed by 6 authors (L.M.A., M.B.B., G.C., E.J., M.J.L., V.P.). The Cochrane Collaboration's criteria[24] was used to determine risk of bias. Each of the 7 risk parameters (plus 2 additional criteria for randomized controlled trials) was judged as *low*-, *unknown*-, or *high risk*. Accuracy of all data was confirmed by at least 2 authors and disagreements were resolved by consensus. Attempts to contact corresponding authors to provide missing data and clarifications were made as needed. Across the accepted articles there was large variability of study methods, including ETT modifications, use of pharmacologic agents, and changes in overall patient management. Based on this variability, we made the *a priori* decision to look only at the control groups/standard of care groups in an attempt to minimize the potential occurrence of confounding variables that may be related to laryngeal injury (Supplemental Table 2). Despite these efforts, a substantial heterogeneity among the accepted studies remained.

Borrowing from the literature, we adapted a 4-step grading rubric to classify laryngeal injuries (Table 1).[25-27] This rubric was updated via consensus validation by 5 authors: 3 laryngologists (L.M.A., S.R.B., A.T.H.), an emergency medicine physician (M.J.L.), and a speech-language pathologist (M.B.B.). We calculated prevalence as the total number of patients with each laryngeal injury or symptom divided by the total number of subjects analyzed for each of these particular outcomes across studies. Post-extubation outcomes not reported were excluded from prevalence calculations. Because all studies did not evaluate the same outcomes relative to either laryngeal injury or patient symptoms, denominators for prevalence calculations differ across categories. Any outcome assessed prior to extubation was not included. Many studies reported voice quality using terminology that was inconsistent across studies. As a result, we report *dysphonia*, *aphonia*, and *hoarseness* separately for purposes of prevalence. Collectively, however, we grouped these symptoms of laryngeal injury as "voice dysfunction" for purposes of discussion. Two additional terms, *pain* and *sore throat*, have similar meanings and were likewise grouped.

Statistical Methods

Pooled estimates of the average patient age and duration of intubation were estimated using linear random effects models including a random intercept for each study, an overall intercept (the pooled estimate) and study-specific, known variance estimates. For studies with average age reported as median and interquartile range or range, the mean and standard deviation were estimated using existing methods.[28] For injury types reported in at least three

studies, similar linear random intercept regression models were used for the log odds of each injury (logit transformation of injury prevalence). The estimated pooled prevalence and 95% confidence intervals were computed by applying the inverse-logit transformation. Similar models were used to compute the prevalence of each symptom reported in at least three studies. For injuries/symptoms reported in only two studies, the prevalence was calculated by dividing the total number of patients with the injury/symptom by the total sample size, with the total taken across the two studies. SAS® version 9.4 (2016, Cary, NC) was used to conduct all analyses.

RESULTS

Search Results

After an original search and three updates, 6754 publications were identified from the 4 databases and other sources. Screening by title and abstract resulted in 160 full-text reviews. After the September 2019 search update, ICU studies were excluded from the search; thus, there is no update to the final count of ICU studies. Of these 160 full-text reviews, 21 surgical studies were accepted (Figure 1) and included 6140 patients from 1 cross-sectional study,[29] 3 cohort studies,[4,6,30] 5 case series,[31-35] and 12 randomized controlled trials (RCT).[7,9,36-45] Of the 12 RCTs, 4 (33%) studies were registered clinical trials with ClinicalTrials.gov (Table 2).[41-44]

Patient Demographics and Presentation

There was 1 (5%) study that did not report the type of surgery performed.[35] The remaining 20 (95%) studies completed surgeries and imposed inclusion/exclusion criteria that did not involve areas associated with the pharynx, larynx, or procedures that may have affected function of either of these two anatomical areas. Studies that included head and neck surgeries largely focused on eye, ear, or nasal procedures. Other studies included surgeries unrelated to the head and neck (e.g., extremities, gynecological, orthopedic, abdominal, vascular).

Six (29%) studies targeted reduction of symptom severity through evaluation of different medications during intubation.[37-42] Four (19%) studies tested changing the shape of the ETT[7,9,44] or its pliability.[43] In all 10 (48%) of these aforementioned studies, prevention of injury and/or symptoms was the goal. The remaining 11 (52%) studies determined prevalence of injury without intervention, assessed various pharmacologic approaches to improve laryngeal exposure, characterized patient symptoms and voice quality, and assessed laryngeal injury as part of this effort.[4,6,29-36,45] The mean patient age was 49 (95% confidence interval [95%CI]: 45, 53) years was similar across the 18 (86%) studies reporting age.[4,6,7,30,31,33-45] The mean intubation duration for 19 (90%) studies[4,6,7,9,29-31,33-36,38-45] that reported this variable was 132 (95%CI: 106, 159) minutes, excluding one study that included the post-operative intubation period with a mean intubation duration of 22 (range: 12 - 52; SD = 8) hours.[7]

Endotracheal Tube Characteristics

There were 16 (76%) studies that reported ETT size,[7,29-31,33-42,44,45] 12 (75%) that distinguished ETT size between the sexes with females receiving an inner diameter 0.5 mm[30,33,35] – 1.0 mm[7,33,37-42,44,45] smaller than males. Most often, males received an 8.0 ETT and females received a 7.0 ETT.[7,37,39-42,44] Four different ETT manufacturers were reported in 11 (52%) studies.[7,32,33,36,37,39,40,42-45] Only 8 (38%) studies reported both ETT size and manufacturer.[7,33,36,37,39,40,42,44]

Post-extubation Laryngeal Evaluation

All studies reported the type of visualization of the larynx and surrounding tissues that was performed. Direct visualization occurred in 2 (10%) studies[9,29] and indirect visualization occurred in 19 (90%) studies (Table 2).[4,6,7,30-45] Of the 19 studies using indirect visualization, 9 (47%) used stroboscopy, allowing for observations specific to vocal fold vibration. Post-extubation assessment was completed immediately in 6 (30%) studies, [9,29,32,34,43,45] ≤24 hours in 12 (60%) studies,[4,6,7,30,33,36-38,40-42,44] and ≤3 days in 1 (5%) study.[39] Two (10%) studies extended initial follow-up beyond 3 days.[31,35] Interpretation of findings was performed in 13 (57%) studies by an otolaryngologist,[7,30,31,35,37-44] in 1 (5%) study by an anesthesiologist,[9] and in 1 (5%) study by both an otolaryngologist and a thoracic surgeon.[6] The remaining 7 (35%) studies did not report the evaluator's training.[4,29,32-34,45]

Post-extubation Laryngeal Injuries – Short Duration Follow-up—Five studies (25%) did not report on the number of patients without laryngeal injury, either due to a requisite period for screening patients with symptoms,[30,35,39] observation of select injury types,[29] or unclear reporting,[6] and reported only individual outcomes. Therefore, prevalence of injury is derived from the 16 (76%) studies that reported patients with and without injury. [4,7,9,31-34,36-38,40-45] Of these, 2052/2328 (80%, 95%CI: 69%, 88%) patients did not present with laryngeal injury post-extubation. Follow-up durations for 2 studies exceeded 4 days and were not considered in this calculation due to the potential for recovery of some injuries within the 4-23 day window.[31,35]

Studies often did not distinguish whether there was co-occurrence of multiple injuries or each injury was isolated. The prevalence reported in this systematic review makes no assumption that each patient experienced a single injury. A high prevalence of minor injury and reduced prevalence of more severe injury was observed (Table 1; Supplemental Table 3). The majority of laryngeal injuries were self-limiting, Grade I injuries. Edema (in various forms) was the most frequently reported injury, with a prevalence ranging 9% - 84% across 9 (45%)[4,6,7,9,36,39,42-44] studies. The most frequently reported moderate (i.e., Grade II) injury was hematoma, with a 4% (95%CI: 2%, 10%) prevalence across 13 (62%) studies. [4,29,31,32,34,37-40,42-45] Severe injuries (i.e., Grade III) were reported in 5 (24%) studies reporting these outcomes.[29,31,32,34,35] These 13 patients included 4 patients with subluxation (prevalence: 0.1%) of an arytenoid cartilage[35,37] and 9 patients with vocal fold paralysis (prevalence: 0.4%, 95%CI: 0.1%, 3%).[31,34,35]

Post-extubation Laryngeal Injuries – Long Duration Follow-up—Initial follow-up in 2 studies was extended beyond 3 days post-extubation, questioning the potential for not

being able to identify injuries that resolved during this period.[31,35] The 210-patient case series by Friedrich completed initial evaluations in 4-9 days post-extubation on all patients with the goal of determining laryngeal injuries post-extubation,[31] but no detail was provided for the distribution of this time. The 3093-patient case series by Yamanaka had the goals of determining the duration of hoarseness and the final outcome of patients with hoarseness lasting >7 days.[35] Laryngoscopic evaluations were only completed on 25 (0.8%) patients with hoarseness lasting >7 days. Of these, 7 (28%) patients were unable to be followed and an additional 2 (8%) patients were not done. Among the 16 (64%) remaining patients who were evaluated post-extubation, the median follow-up time was 13.5 (interquartile range: 8, 15) days.

Post-extubation Patient Symptoms—There were 16 (76%) studies that reported post-extubation symptoms of laryngeal injury.[6,7,9,30,34-45] However, the specific types of symptoms were inconsistently reported across studies (Table 3; Supplemental Table 4). The most frequently reported symptom was hoarseness, with a 27% (95%CI: 12%, 50%) prevalence.[6,7,34-45] Pain and sore throat were studied in 11 (52%) studies, reporting a 38% (95%CI: 0.5%, 99%) prevalence and 27% (95%CI: 16%, 42%) prevalence, respectively.[6,7,9,30,34,39-43,45] Although dysphagia was not studied widely, only 3 (14%) studies, it had a large average prevalence of 43% (95%CI: 21%, 68%) prevalence.[6,7,45] No additional information was provided about the impact of dysphagia on patient safety, (i.e., aspiration, aspiration pneumonia) or other patient outcomes (e.g., altered diets). Other areas of inquiry, such as cough, aphonia, and dyspnea were infrequently reported.

Methodological Quality/Risk of Bias

Methodological quality is summarized as risk of bias assessment (Table 4). Definitions for each of the assessment categories are provided in Supplemental Table 5. All studies provided adequate rationale and clear objectives. There were 2 (10%) studies, both RCTs, that presented with low risk of bias for all 9 of the RCT measures.[43,44] An additional 7 (33%) studies had only 1 unknown risk of bias reported.[6,37-42] Reporting bias was judged as low risk for all studies. There was 1 study that had a high risk for avoidance bias.[45] There were several weaknesses. Perhaps the most concerning weakness was detection bias, with unknown risk of bias in 4 (19%) studies[4,6,31,32] and high risk of bias in 5 studies.[29,30,34-36] There was an unknown risk of sampling bias in 7 (33%) studies.[4,9,29,31-34] Of the 12 RCTs, 3 (25%) had unknown risk of bias with randomization methods[7,9,45] and 10 (83%) had unknown allocation concealment methods.[7,9,36-42,45] Government/institution/foundation support was reported by 2 (10%) studies[9,44] and commercial support was reported by 1 (5%) study.[29] One (5%) study reported both institution and commercial support.[37] The 2 (10%) studies reporting commercial support both received equipment to assist with obtaining outcomes[29,37] and one that additionally received financial support for liability insurance.[37]

DISCUSSION

This systematic review focused on the prevalence of the types of laryngeal injury and their severity subsequent to endotracheal intubation during surgery. The 21 studies reporting on 6140 patients accepted for review demonstrated considerable heterogeneity of patient

populations, study methods, and reported outcomes. The most remarkable finding was that although laryngeal injury and its symptoms are common consequences of intubation after surgery, an overwhelming majority of patients will emerge post-extubation from short-term (i.e., average of 2 hours) surgeries *without* laryngeal injury. Most patients who experience injury will be confined to self-limiting, soft tissue injuries (Grade I). Although more severe injuries (Grades II and III) are reportedly rare events, they should not be overlooked, either because of the functional consequences (i.e., dysphonia, dysphagia) or the potential for medical legal action.[46]

Several studies omitted reporting ETT size[4,6,9,32,43,45] and nearly half did not report the ETT manufacturer.[4,6,9,29-31,34,35,38,41] Seven (33%) studies[4,9,29,32-34,45] were written before 2000 that, although not detailed, may have used different ETT materials or high pressure cuffs compared with other accepted studies, potentially affecting outcomes.[47] These omissions limit this study's ability to offer conclusions about the impact of ETT size on laryngeal injury and its severity. Until recently, there was virtually no link between ETT size and laryngeal injury. A study in the ICU literature suggests that a 7.0 ETT may be protective for laryngeal injury compared to ETT sizes 7.5 and 8.0.[12] With 88% prevalence of no injury and all studies that reported size use ≥7.5 ETTs, clinicians may continue using larger ETT sizes. However, the 4-5% of surgeries resulting in moderate-to-severe laryngeal injuries as unintended consequences should give clinicians pause. Future studies should report ETT size, model, and manufacturer in their analyses, with the broader intentions of transparency in reporting and understanding the effects of these characteristics on laryngeal injury.

There do not appear to be guidelines for ETT size during surgery. Smaller size ETTs should be used for routine anesthesia,[48] yet all reviewed studies used similar size ETTs to those in our previous systematic review of 9 ICU studies.[11] Recently published guidelines for intubation during critical care explicitly state that a full discussion of ETT size is "beyond the remit of this guideline" (p. 337).[49] With short durations and minimal expectation of intubation post-surgery, it follows that large ETTs are not necessary. The primary purpose of anesthesia delivery during surgery would suggest small ETTs are most appropriate. Moreover, the choice of smaller ETTs reduces concerns for its placement, especially in cases with difficult airways.[48,49]

Considering the frequency of Grade I injuries and voice dysfunction, it is tempting to think the two are associated; however, this is not an accurate conclusion. Our raw data suggest that voice dysfunction is independent of laryngeal impairment and dysphagia. Additionally, there is no apparent association between anatomical findings and subjective complaints of hoarseness[36,42] or dysphagia.[6,7] Updated guidelines for dysphonia after surgery state that new onset dysphonia after surgery "should have an expedited laryngeal evaluation according to the AAO-HNSF [American Academy of Otolaryngology-Head and Neck Surgery Foundation] guidelines, which recommend that this occur between 2 weeks and 2 months following the surgery" (S13).[18] Two statements later, the guidelines read: "Early evaluation is also recommended for patients with dysphonia after extubation, regardless of duration of intubation, since they are at increased risk of having laryngeal injury, vocal fold paralysis, and aspiration. These patients are all more easily treated if identified early (S13)." Our data support early laryngeal assessment for interventions that are in patients' best interests.

We found that 6/7 (86%) studies[4,9,29,32,34,45] published before 2000 had multiple areas of unknown/high risk of bias, specifically insufficient information for study replication, sampling bias, and detection bias. Additionally, both RCTs during this period provided inadequate information for randomization and allocation concealment.[9,45] After 2000, detection bias and allocation concealment for RCTs continue to be problematic; the remaining 7 parameters were virtually all low risk of bias. Contributors to reducing risk of bias and improved study quality around this time frame are the International Committee of Medical Journal Editors guidelines[50,51] and the U.S. law[52] for publications being followed by the National Institutes of Health.[53] Future studies should consider these frequently updated guidelines and improvements in the clarity and transparency of research publications.

Limitations

We acknowledge several possible limitations. We limited our search to peer-reviewed publications with planned prospective data only. The gray literature that was excluded is characterized by conference abstracts unable to provide sufficient detail for review. Excluded studies, specifically retrospective studies, may have influenced estimates of prevalence. Even with these restrictions in the context of various methods across this relatively small number of accepted studies and the multiple focuses of the accepted studies, the subjects analyzed in this review were well-controlled *a priori*. We only permitted the analysis of control groups/standard of care groups, thus the strength of our findings for each injury grade is not likely to be substantially altered and largely agrees with the extant literature. Another potential limitation is that each of these studies were planned surgeries. Although we did not exclude studies based on duration of the surgery, we did not find surgeries that had longer durations while meeting other inclusion/exclusion criteria. These findings are not likely generalizable to longer duration surgeries. Despite these limitations, we believe this systematic review makes a unique contribution to the literature surrounding airway management of surgical patients by addressing post-extubation laryngeal injury, its prevalence and severity, and its clinical signs and symptoms, offering several areas for additional research and clinical action.

CONCLUSIONS

Short durations of intubation are associated with laryngeal injuries, but are generally mild. Moderate and severe injuries are rarer. Still, astute clinical observation will identify injuries leading to early treatment with the best potential outcomes. Best-practice guidelines for laryngeal assessment post-extubation from surgery are needed. Based on these data, a postoperative screening/assessment should occur for surgeries longer than 2 hours. Such an assessment will help facilitate the timely recognition and early interventions for serious laryngeal injury and its associated sequalae.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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GLOSSARY OF TERMS

95%CI	95% confidence interval
AAO-HSNF	American Academy of Otolaryngology-Head and Neck Surgery Foundation
CINAHL	Cumulative Index of Nursing and Allied Health Literature
ETT	endotracheal tube
ICU	intensive care unit
LMA	laryngeal mask airway
mm	millimeter(s)
NR	not reported
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RLN	recurrent laryngeal nerve
SD	standard deviation

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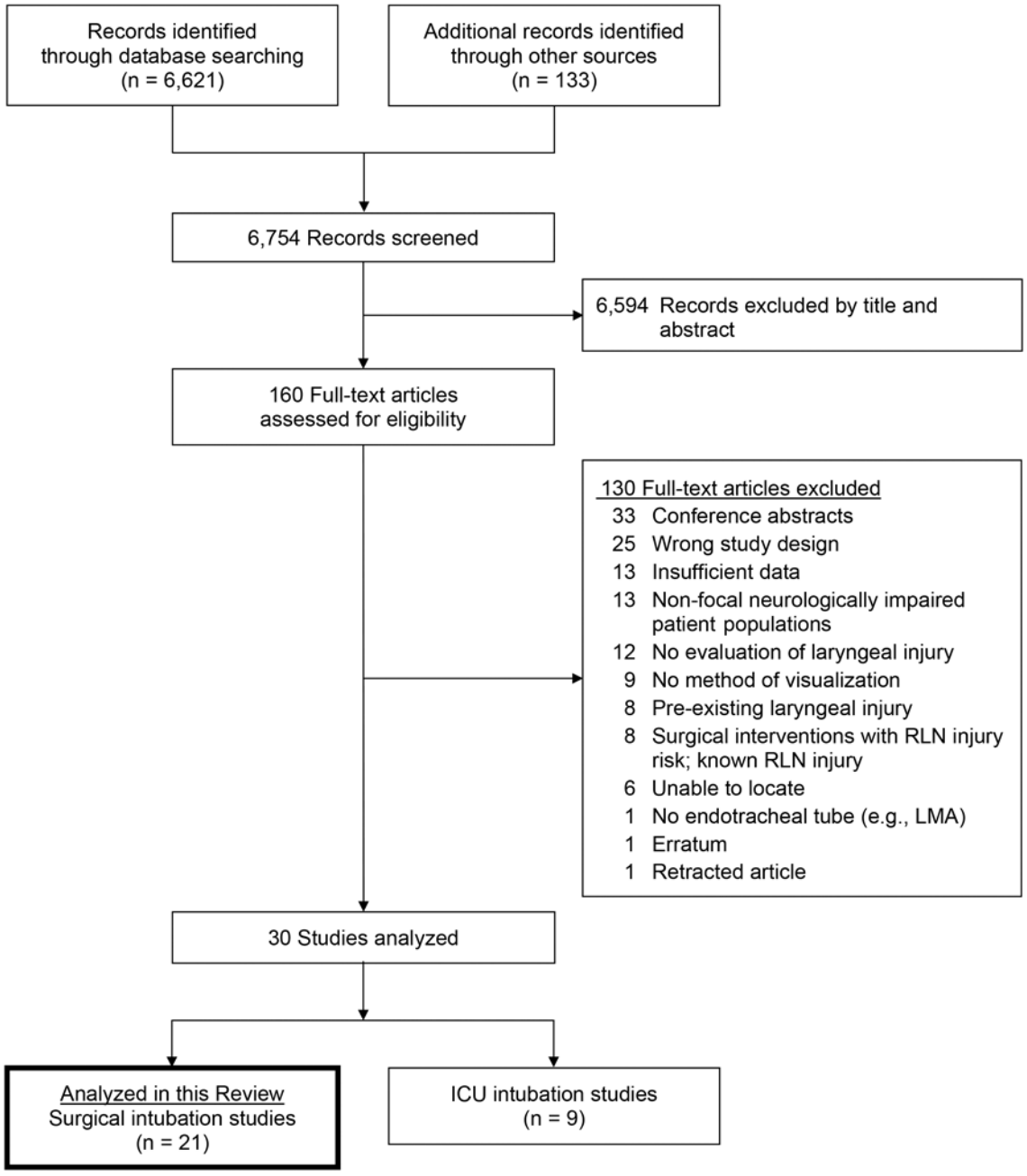

Figure 1. Study selection flowchart.

Abbreviations: LMA, laryngeal mask airway; RLN, recurrent laryngeal nerve

Table 1.

Prevalence[a] of laryngeal injury by grade after extubation.

GRADE/Injury	Patients	Study N	Studies Reporting: Count (%)	Prevalence: % (95%CI)
GRADE 0				
No injury	2052	2328	16 (76)	80 (69, 88)
GRADE I				
Arytenoid edema	42	50	1 (5)	84
Vocal process(es) erythema	15	23	1 (5)	65
Tracheal irritation	52	100	1 (5)	52
Interarytenoid edema	34	73	2 (10)	47
Vocal process(es) edema	4	23	1 (5)	17
Reinke space edema	7	53	1 (5)	13
Edema	91	574	8 (38)	11 (3, 35)
Interarytenoid erythema	2	23	2(10)	9
Post-cricoid edema	2	23	1 (5)	9
Erythema	59	581	5 (24)	8 (2, 30)
Subglottic mucosa erythema	2	123	2 (10)	2
GRADE II				
Thickening of vocal folds	16	116	3 (14)	10 (0.3, 83)
Ulceration	10	100	1 (5)	10
Inter-arytenoid fibrin	11	123	2 (10)	9
Vocal process(es) fibrin	2	23	1 (5)	9
Hematoma, petichiae	122	2368	13 (62)	4 (2, 10)
Granuloma/granulation	3	186	2 (10)	2
Laceration	12	1475	2 (10)	1
Vocal process(es) ulceration	0	23	1 (5)	0
GRADE III				
Paralysis	9	3878	4 (19)	0.4 (0.1, 3)
Subluxation	4	4093	2 (10)	0.1

Abbreviation: CI, confidence interval

[a]Estimated average prevalence (95% confidence intervals) were computed by applying the inverse-logit transformation. Confidence intervals were calculated only for injuries reported by ≥3 studies. Raw data are available in Electronic Supplementary Material 3.

Table 2.

Summary of included studies.

Author/Year	Country	Study Design	Number of patients analyzed[a]	Mean Patient Age (years)	ETT size	Method of Visualization	Intubation Duration (minutes)
Alexopoulos 1983[9]	Sweden	RCT	100	NR	NR	Direct	180
Baillard 2005[30]	France	Cohort	612	49	7.0-7.5	Indirect	120
Beckford 1990[4]	United States	Cohort	9	33	NR	Indirect	66
Böttcher 2014[36]	Germany	RCT	53	48	7.0-8.5	Stroboscopy	98
Friedrich 2000[31]	Germany	Case Series	210	57	7.5-8.5	Indirect	145
Geraci 2013[6]	Italy	Cohort	50	57	NR	Indirect	160
Heidegger 2007[37]	Switzerland	RCT	129	54	7.0-8.0	Indirect	NR
Kambič 1978[32]	Yugoslavia	Case Series	1000	NR	NR	Stroboscopy	NR
Lesser 1987[33]	Wales	Case Series	5	48	8.0-9.0	Indirect	80
Mencke 2003[38]	Germany	RCT	36	48	7.5-8.5	Stroboscopy	65
Mencke 2006 (Rocuronium)[39]	Germany	RCT	150	50	7.0-8.0	Stroboscopy	93
Mencke 2006 (Timing)[40]	Germany	RCT	25	39	7.0-8.0	Stroboscopy	146
Mencke 2013[41]	Germany	RCT	29	49	7.0-8.0	Stroboscopy	94
Nordang 2016[7]	Sweden	RCT	22	58	7.0-8.0	Indirect	1320
Ovari 2017[42]	Germany	RCT	87	51	7.0-8.0	Indirect	98
Peppard 1983[34]	United States	Case Series	475	47	8.0-9.0	Indirect	120
Seo 2016[43]	Korea	RCT	70	57	NR	Indirect	194
Sørensen 2013[44]	Denmark	RCT	55	49	7.0-8.0	Indirect	120
Walts 1980[29]	United States	Cross Sectional	100	NR	6.0-9.5	Direct	156
Yamanaka 2009[35]	Japan	Case Series	3093	53	7.5-8.0	Stroboscopy	283
Zimmert 1999[45]	Germany	RCT	22	29	NR	Indirect	87

Abbreviations: ETT, endotracheal tube; NR, not reported; RCT, randomized controlled trial

[a]Reflects the number of patients meeting inclusion/exclusion criteria for this systematic review, and therefore analyzed and reported in this systematic review.

Table 3.

Prevalence[a] of signs/symptoms reported after extubation.

Sign/Symptom	Patients	Study N	Studies Reporting: Count (%)	Prevalence % (95% CI)
dysphagia	41	95	3 (14)	43 (21, 68)
pain	91	670	4 (19)	38 (0.5, 99)
cough	39	123	2 (10)	32
sore throat	363	1427	10 (48)	27 (16, 42)
hoarseness	1173	4297	14 (67)	27 (12, 50)
dysphonia	31	491	3 (14)	17 (0.0, 99)
laryngeal dyspnea	15	123	2 (10)	12
aphonia	2	55	1 (5)	4

Abbreviation: CI, confidence interval

[a]Estimated average prevalence (95% confidence intervals) were computed by applying the inverse-logit transformation. Confidence intervals were calculated only for injuries reported by ≥3 studies. Raw data are available in Electronic Supplementary Material 4.

Table 4.

Risk of bias assessment.

Reference	Study Type	Rationale	Clear Objective(s)	Selection Criteria	Replication	Sampling	Randomization	Allocation Concealment	Detection Bias	Attrition Bias	Avoidance Bias	Reporting Bias	Government/ Institutional/ Foundation Support	Commercial Support	Registered Clinical Trial[a]
Alexopoulos 1983[9]	RCT	🟢	🟢	🟢	🟢	🟡	🟡	🟡	🟢	🟢	🟢	🟢	✓		
Baillard 2005[30]	Cohort	🟢	🟢	🟢	🟢	🟢			🔴	🟢	🟢	🟢			
Beckford 1990[4]	Cohort	🟢	🟢	🟢	🔴	🟡			🟡	🔴	🟢	🟢			
Böttcher 2014[36]	RCT	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🔴	🟢	🟢	🟢			
Friedrich 2000[31]	Case Series	🟢	🟢	🟢	🟡	🟡			🟡	🟢	🟢	🟢			
Geraci 2013[6]	Cohort	🟢	🟢	🟢	🟢	🟢			🟡	🟢	🟢	🟢			
Heidegger 2007[37]	RCT	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢	✓	✓	
Kambič 1978[32]	Case Series	🟢	🟢	🟡	🟡	🟡			🟡	🟢	🟢	🟢			
Lesser 1987[33]	Case Series	🟢	🟢	🟢	🟢	🟡			🟢	🟢	🟢	🟢			
Mencke 2003[38]	RCT	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢			
Mencke 2006 (Rocuronium)[39]	RCT	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢			
Mencke 2006 (Timing)[40]	RCT	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢			
Mencke 2013[41]	RCT	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢			✓
Nordang 2016[7]	RCT	🟢	🟢	🟢	🟢	🟢	🟡	🟡	🟢	🟡	🟢	🟢			
Ovari 2017[42]	RCT	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢	🟢	🟢			✓
Peppard 1983[34]	Case Series	🟢	🟢	🟢	🟡	🟡			🔴	🟢	🟢	🟢			
Seo 2016[43]	RCT	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢			✓
Sørensen 2013[44]	RCT	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢	✓		✓
Walts 1980[29]	Cross-sectional	🟢	🟢	🟢	🟢	🟡			🔴	🟢	🟢	🟢		✓	
Yamanaka 2009[35]	Case Series	🟢	🟢	🟢	🟢	🟢			🔴	🟢	🟢	🟢			
Zimmert 1999[45]	RCT	🟢	🟢	🟢	🟢	🟢	🟡	🟡	🟢	🔴	🔴	🟢			

Key: 🟢 = low risk of bias; 🟡 = unknown risk of bias; 🔴 = high risk of bias.

[a] All registered trials were registered with ClinicalTrials.gov.

Abbreviation: RCT, randomized controlled trial