Endotracheal intubation using videolaryngoscopy versus conventional direct laryngoscopy: a randomized multiple cross-over cluster trial

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Background: Securing airways is a fundamental priority for anaesthesiologists. Severe airway complications are rare, but more than 14 % of the events associated with airway management in the operating room led to death or brain damage.[1,2] Even when ultimately successful, difficult intubation is associated with significant patient morbidity and mortality. Although anesthesiologists nearly always ultimately succeed in intubating the trachea, multiple intubation attempts are common, occurring in 8% of patients.[3] Repeated intubation attempts are clearly associated with respiratory and hemodynamic complications, including hypoxemia, cardiac arrest, regurgitation, aspiration, and airway trauma.[4-6]

Direct laryngoscopy (DL) remains by far the most common primary method for endotracheal intubation. But even in experienced hands, additional tools are sometime needed.[7-9] Videolaryngoscopes are among the most common alternatives or supplements to direct laryngoscopy. The method was introduced about two decades ago and has gained wide acceptance because videolaryngoscopes improve glottic visualization[10-12] which may improve first-pass intubation success rate and reduce complications.

While it is clear that videolaryngoscopy improves glottic visualization, it is far less obvious that first-pass intubation is more likely than with direct laryngoscopy.[10,12] Several studies reported that videolaryngoscopy improved vocal cord visualization, but prolonged the time required for intubation and increased the number intubation attempts.[10,12,13] In a trial with ICU patients, videolaryngoscopy not only failed to improve first-attempt intubation success, but provoked severe complications including hypoxemia, cardiac arrest, cardiovascular collapse, and death.[14] In contrast, other trials confirm improved glottis visualization and report improved first-pass success without an increase in complications.[15-17] In a recent Cochrane review of more than 7,000 patients with and without difficult airways, videolaryngoscopy was associated with fewer complications (e.g., laryngeal or airway trauma, postoperative hoarseness, hypoxia), fewer failed intubations, and no increase in the time required for intubation.[18] Nonetheless,

videolaryngoscopes are still usually considered alternative airway devices rather than an initial intubation method.

Whether using videolaryngoscopes as the initial operating room intubation device reduces intubation attempts remains unclear. Current literature is based on varying study settings including manikins, emergency department patients, intensive care patients, and out-of-hospital situations.[13,19,20] Provider experience also varied considerably, ranging from novice physicians to paramedics to nurse anesthetists to highly skilled anesthesia attendings.[6,12,20,21] Intubation indications also varied, with reports being restricted to cardiopulmonary resuscitation, emergency intubation, anticipated easy intubation, etc. Interpretation is further complicated by use of various videolaryngoscope devices, not always in the appropriate sizes.[11-13,16,19-23]

Most previous trials have been based on dubious intermediate markers such as glottic visualization or time-to-intubation that may correlate poorly with clinically important outcomes. Consequently, current evidence precludes defensible analysis of clinically meaningful outcomes in the standard operating room setting. No published studies were powered to evaluate the number of intubation attempts, a clearly important outcome. The extent to which videolaryngoscopes might facilitate intubation in surgical patients during routine clinical practice therefore remains unclear. The question is important because videolaryngoscopes are more expensive than conventional direct laryngoscopes. The additional cost might be justified — but only if video systems improve intubation success and reduce airway trauma.

Specific Aims:

Primary Aim 1: Assess the effect of using a videolaryngoscope versus direct laryngoscope for the initial laryngoscopy on the number of intubation attempts in patients having cardiac, thoracic, or vascular surgery.

Primary Hypothesis 1: Fewer intubation attempts are required when initial laryngoscopy is performed with a videolaryngoscope rather than a direct laryngoscope in patients

having cardiac, thoracic, or vascular surgery. Any reduction in intubation attempts will be considered clinically meaningful.

Primary Outcome: The number of intubation attempts with the initial laryngoscopy instrument.

Secondary Aim 1: Compare intubation failure rates with videolaryngoscopy and conventional direct laryngoscopy, with failure defined by the clinician switching to an alternative laryngoscopy method.

Secondary Hypothesis 1: There are fewer intubation failures when laryngoscopy is initially attempted with a videolaryngoscope rather than a direct laryngoscope. Any reduction in intubation failures will be considered clinically meaningful.

Secondary Outcome 1: Intubation failure, defined by the clinician switching to an alternative laryngoscopy method.

Secondary Aim 2: Compare airway and dental injuries when laryngoscopy is initially attempted with a videolaryngoscope rather than a direct laryngoscope.

Secondary Hypothesis 2: A composite of airway and dental injuries is less common when laryngoscopy is initially attempted with a videolaryngoscope than with a direct laryngoscope. A reduction with a number-needed-to-treat <100 will be considered clinically meaningful.

Secondary Outcomes 2: Any dental and/or airway injury, defined as any bleeding or apparent injury.

Exploratory Hypothesis 1: Intubation assisted by videolaryngoscope provokes less hypertension and tachycardia than direct laryngoscopy. Differences in mean arterial pressure >10 mmHg and/or in heart rate of at 10 beats/minute will be considered clinically meaningful.

Exploratory Outcomes 1: Maximum mean arterial pressure and heart rate in the 5 minutes after intubation.

Methods: This research project will be conducted with Cleveland Clinic IRB approval and waived patients consent. (see Human Subjects section for justification). The trial will be registered at ClinicalTrials.gov (NCT04701762, date of registration January 8 2021) before enrolling any patients. A full statistical analysis plan will be developed before any data are evaluated. Reporting will be consistent with the CONSORT guidelines for pilot trials.

Design: The proposed quality improvement project will be conducted in an isolated set of 22 operating rooms (J operating suites) at the Cleveland Clinic Main Campus which is largely staffed by a consistent team of anesthesia attendings, nurse anesthetists and anesthesia residents and fellows with variable level of experience. Most operations in this suite are cardiac, thoracic, or vascular surgeries. Nearly all require general anesthesia, and most patients are hospitalized at least overnight.

We plan a cluster randomized multiple crossover quality improvement project. The J operating suites will be divided into 2 separate clusters consisting of 11 operating suites each (cluster 1: operating suites 60 to 70, and cluster 2: operating suites 71 to 81). Clusters were formed by physical proximity to make it as logistically feasible as possible to conduct the trial.

Randomization will consist of randomizing cluster 1 to use either videolaryngoscope or direct laryngoscope, and cluster 2 to the alternative device in one-week blocks.

Randomization, 1:1 and unstratified, will be based on computer-generated codes maintained in a web-based system that investigators will access one day before each new treatment block begins. Randomization allocations will be verbally communicated to anesthesia personnel directly and by signs prominently displayed on each anesthesia machine. In previous similar trials, compliance with designated allocations exceeded 97%.

Design notes: Cluster randomized multiple crossover cluster trials are analogous to individual patient crossover trials, except that each cluster is crossed over to the other treatment in the next period instead of individual patients crossing over. They differ from cluster randomized trials (CRT) in that each cluster receives each treatment multiple times instead of each cluster only receiving one of the interventions during the trial.

Subject selection: We propose to enroll adults scheduled for elective or emergent cardiac, thoracic, or vascular surgery in the designated operating room suite who require endotracheal intubation for general anesthesia. We will enroll male and female patients of any race and ethnicity. Using the videolaryngoscope as the first line airway device is likely to be beneficial and unlikely to augment risk.

Inclusion criteria:

1. Elective or emergent surgery requiring oral endotracheal intubation for general anesthesia.

Exclusion criteria:

1. The attending anesthesiologist prefers a specific approach for a particular patient;
2. Awake fiberoptic intubation is clinically indicated;
3. Insertion of double-lumen tube.

Protocol: There will be no restrictions on anesthesia management, and anesthesia providers will be free to use any type of general anesthesia, supplemented by any type of regional anesthesia including neuraxial and peripheral nerve blocks. Fluid management, type and dosage of anesthesia medications, and postoperative analgesia will also be per clinical preference.

Our clinical routine is to intubate patient's supine on the OR table. Patients will be pre-medicated with midazolam 0-2 mg IV, as clinically appropriate. Patients will be pre-oxygenated until the fraction of expired oxygen exceeds 80%. General anesthesia will be induced as preferred by the attending anesthesiologist, usually with a combination of lidocaine 1 mg/kg, propofol 1-3 mg/kg or etomidate 0.2-0.3 mg/kg, fentanyl 1-3 μg/kg, and

succinylcholine 1.5 mg/kg or rocuronium 1.0 mg/kg. Our routine practice is to perform endotracheal intubation after confirming adequate muscle relaxation. In qualifying patients, initial laryngoscopy will be performed using one of the following methods:

1. Direct laryngoscopy with an appropriately sized Macintosh or Miller blade (usually size 3 or 4);
2. Indirect laryngoscopy using a GlideScope videolaryngoscope with an appropriately sized blade (usually size 3 or 4). The GlideScope (Verathon, Bothell, WA 98011) is an FDA-cleared commercially available portable videolaryngoscope.[24-30]

Intubations will be performed with a regular endotracheal tube selected by the responsible clinician, usually having an internal diameter of 7-8 mm. Endotracheal tubes can be equipped with a stylette, per clinical preference. The GlideScope or the Macintosh/Miller blade will be introduced into oral cavity according to manufacturer recommendations and routine practice. Minor airway manipulation procedures including BURP or Sellick maneuvers will be allowed to improve visualization of the vocal cords.

If the initial intubation attempt fails, the endotracheal tube will be removed. Adjustments of patient's position and/or tube stylette are allowed as clinically appropriate. There is no limitation regarding intubation attempts, but our routine is to switch to an alternate intubation technique after a maximum of 3 failed attempts. Further airway management will follow clinical assessment by the attending anesthesiologist. Anesthesiologist will be permitted to switch to an alternative method at any time.

Once the trachea is intubated, the tube will be connected to the anesthesia circuit and general anesthesia maintained as clinically indicated. At the end of surgery, patients will be transferred to the post anesthesia care unit or intensive care unit.

Video recording for teaching purposes: a training video of the intubation procedure using the GlideScope videolaryngoscope will be produced. This video will be used for training purposes of the clinical personnel involved in this clinical trial only and will not be shared with anyone outside CCF. Patients will be entirely de-identified. Separate and individual informed consent using the CCF "Photograph, Film or Vocal recording release" will be obtained in up to a maximum of three patients.

Measurements: All data will be obtained from electronic anesthesia and hospital records. No tests or evaluations will be done specifically for this trial. Preoperative airway characteristics and difficulties encountered during anesthetic induction will be recorded per routine (*table 1*). Demographic and morphometric characteristics will be obtained from the electronic records including age, sex, race, and body mass index. Type of surgery will be characterized from ICD-10 codes using AHRQ Clinical Classifications Software. All routine anesthetic variables, including medications, will be recorded by routine by our electronic anesthesia record keeping system. We will also capture the level of training of the person making the first intubation attempt and the final intubation attempts (if a switch of anesthesia providers occurred).

Table 1:

Preoperative airway characteristics	Neck- full range of motion
	Limited neck extension
	Limited neck flexion
	Limited neck extension and flexion
	Short neck
	Short thyromental distance
	Small mouth opening
	Non-compliant submandibular space
	Beard presents
Difficulties encountered during anesthesia induction	Anterior larynx
	Expected difficulties
	Large epiglottis
	Large tongue
	MAC safe cannula
	Poor jaw range of motion
	Poor neck range of motion

	Recessed chin
	Sniffing position
	Stylette required
	Unexpected difficulties

Per our clinical routine, an initial attempt will be defined by insertion of a laryngoscope blade and/or endotracheal tube into a patient's mouth. Subsequent attempts will be defined by re-insertion of an endotracheal tube, or insertion of the same or a new laryngoscope blade. Attempts will be recorded per routine by anesthesia providers in the electronic record.

Intubation failure will be defined by the responsible clinician switching to an alternative laryngoscopy device for any reason at any time, or by more than 3 intubation attempts.

A*irway injury* will be defined as any bleeding or apparent injury to the lips, mouth, pharynx, vocal cords, or other airway structures recorded by the anesthesia team.

Dental injury will be defined as any apparent injury to the teeth as recorded by the anesthesia team.

Limitations and anticipated difficulties:

The proposed study will be by far the largest randomized trial of airway management. It will include patients with a broad range of airway characteristics, only excluding patients with airway pathologies so severe that responsible clinicians prefer an initial fiberoptic intubation. Our finding should therefore be broadly generalizable to adult surgical patients.

This project will be performed in the J operating rooms area of the Cleveland Clinic Main Campus. This area includes 22 operating rooms, which is largely staffed by a consistent team of anesthesia attendings and nurse anesthetists. We have substantial experience with large studies in this surgical area, and have had consistently excellent collaboration with the entire anesthesia team, along with the surgeons.

We selected the GlideScope videolaryngoscope because it is currently used routinely at the Cleveland Clinic and all anesthesia personnel are familiar with the device. Finally, GlideScope videolaryngoscopy devices and blades have been donated by the manufacturer so there will be no cost to patients or the institution.

Statistical Analysis:

We will assess the balance of randomized groups (videolaryngoscopy vs. direct laryngoscopy) on baseline and demographic characteristics using the absolute standardized difference (ASD), defined as the absolute difference in means, mean ranks, or proportions divided by the pooled standard deviation. Any characteristics with ASD > maximum of 0.10 and $1.96\sqrt{(n_1+n_2)\mathrm{x}(n_1n_2)}$ will be considered imbalanced and will be adjusted for in the primary and secondary analyses.

All primary and secondary analyses will use the modified intent-to-treat principle, including all randomized patients who received any of the study. We will conservatively assign all missing outcome values as the highest possible score in the control group (direct laryngoscopy) and the lowest possible score in the treatment group (GlideScope videolaryngoscopy) for all primary and secondary analyses. Assumptions of statistical tests will be assessed using graphical and statistical methods.

For the primary outcome, number of intubation attempts will be calculated as the number of attempts with either device, independent of whether or not a patient was crossed over to the other device due to failure with the randomized device. The ordinal categories will be 1, 2, 3, and > 3 attempts. We will assess the effect of videolaryngoscopy vs. direct laryngoscopy on the number of intubation attempts using a generalized linear mixed effects cumulative logit model in which we consider the outcome to be ordinal and consider the operating room within cluster as a random effect. In sensitivity analyses we will assess the treatment effect using a Wilcoxon-Mann-Whitney test and a proportional odds logistic regression model, if the assumption of proportional odds holds. In all analyses, we will adjust for variables imbalanced at baseline.

For the secondary (binary) outcomes of 1) intubation failure and 2) collapsed composite of any airway or dental injury we will assess the effect of videolaryngoscopy vs. direct laryngoscopy using a generalized linear mixed effects model in which we consider the outcome to be binary and consider the operating room within cluster as a random effect.

For exploratory outcomes of maximum mean arterial pressure and heart rate in the 5 minutes after intubation we will conduct analogous linear mixed effects models for continuous variables (i.e., using identity link). Sensitivity analyses will include simple Mann-Whitney or t-test, as appropriate. As with the primary analysis, we will adjust for any imbalanced confounding variables using analogous methods.

Treatment effect heterogeneity (treatment effect modification). In exploratory analyses we will assess whether the treatment effect on the primary outcomes of intubation success on the first attempt varies across levels of pre-specified baseline variables by assessing the treatment-by-covariate interaction in the relevant model. Factors of interest include experience level (experience versus not experienced), patient's sex, patient's body mass index (BMI), emergency vs. elective surgeries, full neck range-of motion, limited neck extension, limited neck flexion, short neck, history of previous difficult intubation, short thyromental distance, non-compliant submandibular space, beard presents, anterior larynx, a priori expected difficulties during airway management, large epiglottis, large tongue, poor jaw range of motion, poor neck range of motion, recessed chin, and stylette required.

An important potential effect modifier will be the learning curve of anesthesiologist on their skill with GlideScope videolaryngoscopy. We expect about a 3-month learning curve for the average provider. We will therefore assess the interaction between the treatment effect and time since start of the trial, dichotomized as early (first 3 months) versus late (after initial 3 months) on the primary outcome of number of intubation attempts. This sensitivity analysis will also include graphical moving average displays of the proportion

over time with the outcome in each treatment group, and well as displays of the treatment effect over time (independent of the 3-month grouping).

Interim Analyses. We will conduct interim analyses for efficacy and futility at each 25% of the planned enrollment using a group sequential design with a gamma spending function, with gamma parameter of -4 for efficacy and -1 for futility. Assuming the alternative hypothesis is as specified below in Sample Size Considerations, there will be a cumulative 9.4% probability of crossing a stopping boundary at the first look, 40% through the 2nd look, 78 % through the 3rd look and 100% by the last. Stopping boundaries will *not* be binding – the decision to stop or continue the trial will be made by the DSMB which will consider all available information in their decision.

Sample size considerations. Sample size is based on the primary outcome, the number of intubation attempts (with either device). About 5,000 operations per year will be performed during the anticipated 3-year enrollment period. Based on a previous study, we expect that about 10% of patients may require more than 1 intubation attempt in the direct laryngoscopy group versus about 4% in the videolaryngoscopy group.[31] (Direct laryngoscopy 1 attempt: 90%, 2 attempts: 4%; Videolaryngoscopy 1 attempt: 96%, 2 attempts: 4%). However, we plan the study to detect a slightly smaller effect, which also would be clinically relevant.

We assume for sample size calculation that the proportion having 1, 2, 3 or more than 3 attempts will be 0.90, 0.04, 0.03, 0.03 in the direct laryngoscopy group and 0.92, 0.04, 0.02, 0.02 with videolaryngoscopy. To detect this difference or a larger one with 90% power at the 0.05 significance level with a Mann-Whitney test we would need a total of 8,800 patients, before accounting for interim analyses or within-cluster correlations. Accounting for a small within-cluster correlation of 0.01 and even smaller within-cluster

between-period correlation of 0.009, the required total sample size [32] is 13,112. Further adjustment for interim analyses requires a maximum total of 14,943 patients.

Internal Pilot Study to Assess Sample Size Assumptions. At the first interim analysis we will re-assess the distribution of the primary outcome in the direct laryngoscopy group only (since the prevalence can be considered a nuisance parameter analogous to standard deviation for a continuous outcome) as well as the assumed within-cluster and within-cluster between-period correlation. We will resize the study if the required N based on the revised parameter estimates is noticeably higher than originally planned for the same planned treatment effect.

Executive summary: Securing the airway is fundamental in surgical patients; a key component is endotracheal intubation, which is usually easy but sometime extraordinarily difficult. Direct laryngoscopy is generally used as the first-line airway device. Videolaryngoscopy improves airway visualization, but it remains unclear whether videolaryngoscopy reduces the number of intubation attempts. We therefore propose a large, robust trial powered to determine whether videolaryngoscopy reduces the need for multiple intubation attempts.

Significance: Most surgical patients require endotracheal intubation. Although relatively rare, difficulties during endotracheal intubation can cause substantial patient morbidity including respiratory and hemodynamic instability, hypoxemia, cardiac arrest, regurgitation, aspiration, and airway trauma. The proposed study will extend available information and will determine whether videolaryngoscopy is superior to direct laryngoscopy, and whether videolaryngoscopy should be used initially in routine practice.

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Chronological List of changes:

Version 7 (march 27, 2022)

- A sensitivity analysis has been added to the statistical methods.

Version 6 (May 19, 2021)

- The ClinicalTrials.gov identifier has been added.
- The paragraph regarding video recording was updated.
- The definition of intubation attempts have been updated and specified to reflect current routine practice.

Version 5 (October 6, 2021)

- Several Co-investigators have been added.
- Video recording for teaching purposes has been added.
- The ClinicalTrials.gov identifier has been added.
- The definition of intubation attempts have been updated and specified to reflect current routine practice.

Version 4 (November 3, 2020)

- Title: ”quality improvement project” was replaced by “research project”
- Several Co-investigators have been added.
- Design: we changed the isolated set of operating rooms to the J operating suites, consisting of 22 operating suites (2 are currently not in use) and used for cardiac, thoracic and vascular procedures.
- We further clarify, that we will divide the J OR’s in 2 separate clusters.
- Inclusion criteria, we now enroll adults having cardiac, thoracic, or vascular surgery.
- Exclusion, we now specify, that patient requiring a double lumen tube are excluded.

- Methods: etomidate was added as an alternate induction medication
- Direct laryngoscopy. Using a Miller blade is now added as an alternative to the Macintosh blade.
- Sample size considerations: number of surgeries are adapted to about 5.000 per year and the duration of this project for up to 3 years.
- The sections on statistical analysis and *Treatment effect heterogeneity* have been updated.

Version 3 (May 20th, 2020)

- McGrath videolaryngoscope was replaced by GlideScope videolaryngoscope.
- We added clarification, that this project will be performed in the G operating suite area.

Version 2 (*October 16 2019)*

- Exploratory hypothesis 1 and exploratory outcome 1 was added
- The following paragraph was added "*We will also capture the level of training of the person making the first intubation attempt and the final intubation attempts (if a switch of anesthesia providers occurred)*."

Trial timeline:

08/20/2019	study protocol version 1 finalized
09/11/2019	initial submission of study protocol version1 submitted to IRB
12/24/2020	IRB approval granted (study protocol version 4)
01/08/2021	trial registration on www.clinicaltrials.gov
03/15/2021	Start of clinical training
03/29/2021	First patient enrolled
06/11/2021	AE reported to IRB
02/26/2022	enrollment paused due to transfer of documentation from ARKS to EPIC
03/14/2022	enrollment restarted