Critical Review Form
Therapy

PGY-3

Birenbaum A, Hajage D, Roche S, et al. Effect of Cricoid Pressure Compared With a Sham Procedure in the Rapid Sequence Induction of Anesthesia: The IRIS Randomized Clinical Trial. JAMA Surg. 2018 Oct 17.

Objectives: **"to test the hypothesis that the incidence of pulmonary aspiration is not increased when cricoid pressure is not performed during a RSI [rapid sequence intubation] of anesthesia." (p. E2).**

Methods: **This multicenter, prospective, randomized, noninferiority trial was conducted at 10 hospitals in France between February 2014 and February 2017. Adult patients 18 years of age or older undergoing surgery under general anesthesia and requiring RSI were eligible for enrollment so long as they had < 6 hours of fasting or at least one risk factor for pulmonary aspiration (emergency condition, BMI > 30, previous gastric surgery, ileus, < 48 hours postpartum, diabetic gastroparesis, GERD, hiatus hernia, preoperative nausea/vomiting, or pain). Patients were excluded for pregnancy, participation in another randomized trial, lack of national health insurance, contraindication to cricoid pressure or succinylcholine administration, known pneumonia or pulmonary contusion, upper respiratory tract abnormalities, disorders of consciousness, and need for alternative technique to laryngoscopy.**

Patients were randomized 1:1 to either receive cricoid pressure or to undergo sham cricoid pressure. The primary outcome was the incidence of pulmonary aspiration (either detected visually during laryngoscopy or by tracheal aspiration following tracheal intubation). The sham procedure was considered noninferior if the incidence of pulmonary aspiration was not more than 50% higher (relative risk 1.5). Secondary endpoints included frequency of suspected aspiration pneumonia within 24 hours, difficult tracheal intubation (defined as intubation requiring more than 2 attempts or use of any alternative technique except bougie), and traumatic complications of cricoid pressure.

A total of 3472 patients were recruited from 10 different sites, with one excluded. There were 1735 patients in the cricoid group and 1736 in the sham cricoid group. Six patients in each group were excluded due to minor protocol violations, leaving 1729 patients in the cricoid group and 1730 in the sham group for the primary, per protocol analysis. The mean age was 51 years and 51% were male.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a**	

	similar prognosis?	
1.	Were patients randomized?	Yes. "Patients were randomly allocated in a 1:1 ratio to 1 of the following 2 groups: Sellick group and sham group...The randomization list was computer generated, balanced by blocks of undisclosed size (n = 6), and stratified on the center." (p. E3)
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "Allocation concealment was achieved using a centralized, secure, interactive, web-response system accessible from each study center (Randoweb)." (p. E3)
3.	Were patients analyzed in the groups to which they were randomized?	Yes and no. "The analysis of the primary end point was performed based primarily on the per protocol (PP) population and repeated on the ITT population. The PP population was defined as patients without protocol violation." (p. E3)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with regard to age, gender, presence of risk factors for aspiration, presence of risk factors for difficult intubation, perceived intubation risk, and anesthetic used at time of induction. The authors did not compare the groups based on type of surgery being performed or based on baseline medical comorbidities (aside from those felt to increase risk of aspiration).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. While patients were not specifically blinded, they would have been under general anesthesia at the time of the intervention and hence would not have been aware of which treatment they were receiving. There is no way performance bias on the part of the patients could have influenced the outcomes.
2.	Were clinicians aware of group allocation?	No. "To ensure appropriate blinding of the rest of the team, an opaque cover was applied in both groups masking if the investigator applied pressure. To maintain appropriate blinding in case of difficult tracheal intubation, the unique un- blinded investigator who applied the cricoid pressure could not replace the blind investigator who performed tracheal intubation." (p. E3)
3.	Were outcome assessors aware of group allocation?	No. For the primary outcome, the anesthetist performing the intubation determined who did and

		did not have aspiration based on visualization or tracheal aspiration. For secondary outcomes, the authors do not specify if outcome assessors were blinded to group allocation.
4.	Was follow-up complete?	Mostly yes. For the primary outcome, data were available for all patients randomized within the study. Loss to follow-up was very low for secondary outcomes, with 30 of 1729 lost in the cricoid pressure group (1.7%) and 28 of 1730 were lost in the sham cricoid pressure group (1.6%).
II.	**What are the results ?**	
1.	How large was the treatment effect?	• For the primary outcome, pulmonary aspiration occurred with similar frequency in the cricoid pressure and sham groups, with a relative risk (RR) in both per protocol and ITT analyses of 0.90 (95% CI 0.33 to 2.38). o For the noninferiority analysis, the 1-sided 95% CI was 1.99 in the per protocol analysis and 2.00 in the ITT analysis. This value exceeds the *a priori* noninferiority margin of 1.5, and thus noninferiority was not demonstrated. • The incidence of difficult tracheal intubation was slightly higher in the cricoid pressure group, though this was a rare outcome and did not achieve statistical significance: 4% vs. 3%, RR 1.4 (95% CI 0.99 to 2.0). • There was no difference in the incidence of aspiration or severe pneumonia. • There was no difference in hospital or ICU length of stay.
2.	How precise was the estimate of the treatment effect?	See above. This was a fairly large study with narrow confidence intervals.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	No. This study was conducted in the operating room with patients undergoing elective procedures. The overall incidence of aspiration in this group would likely be much lower than among patients being emergently intubated in the ED using rapid sequence intubation (RSI) (external validity). They did only include patients at higher risk of aspiration (< 6 hours fasting or at least 1 risk factor for aspiration), but these patients would still likely be less prone to aspiration than patients requiring emergent intubation in the ED.

2.	Were all clinically important outcomes considered?	No. The primary outcome of this study (aspiration detected by visualization or tracheal aspirate) was a surrogate outcome of very uncertain clinical significance. The authors did consider the additional patient-oriented outcomes (difficult tracheal intubation, traumatic complications of cricoid pressure, aspiration pneumonia, severe pneumonia), this study was vastly underpowered to detect a clinically significant difference in these outcomes given the very low incidence.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study suggests no benefit to the use of cricoid pressure during elective intubation in the operating room among patients felt to be at higher risk of aspiration, the study was designed as a noninferiority trial, but was done so quite poorly. The authors chose as their margin of noninferiority a value that would be less than the upper limits of the confidence interval if there was truly no difference in the incidence of the outcome between the groups. This likely occurred because the overall incidence of aspiration was much lower than anticipated, but it also means that the study did NOT demonstrate that the sham cricoid procedure was not noninferior to cricoid pressure (i.e. that cricoid pressure may be superior), despite finding no difference in the outcomes. Additionally, the primary outcome evaluated is of very uncertain clinical significance and the study was vastly underpowered to detect a clinically important difference in more meaningful outcomes.

Limitations:

1. **The primary outcome was poorly defined. The authors do not specify how aspiration was diagnosed with tracheal aspirate and do not specify what specific criteria were needed for visualized aspiration.**

2. **The primary outcome of this study (aspiration detected by visualization or tracheal aspirate) was a surrogate outcome of very uncertain clinical significance.**

3. **The patients and setting in this study are very different from our practice environment, and it is unclear if these results would be externally valid when considering emergent intubation using RSI in the ED.**

4. **Despite the performance of a sample size analysis, the incidence of the primary outcome was much lower than anticipated. The end result was that noninferiority**

could not be established despite there being no observed difference in outcomes between the two groups.

Bottom Line:

This large, randomized, double-blind trial found no significant difference in the rates of aspiration between high-risk patients who received cricoid pressure for RSI in the operating room and those who underwent sham cricoid pressure. Unfortunately, due to the low incidence of the primary outcome, the study could not confirm the noninferiority of omitting cricoid pressure.