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Original Contributions

SUCCESS AND COMPLICATIONS OF THE KETAMINE-ONLY INTUBATION METHOD IN THE EMERGENCY DEPARTMENT

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☐ **Abstract—Background: Rapid sequence intubation (RSI), defined as near-simultaneous administration of a sedative and neuromuscular blocking agent, is the most common and successful method of tracheal intubation in the emergency department. However, RSI is sometimes avoided when the physician believes there is a risk of a can't intubate/can't oxygenate scenario or critical hypoxemia because of distorted anatomy or apnea intolerance. Traditionally, topical anesthesia alone or in combination with low-dose sedation are used when physicians deem RSI too risky. Recently, a ketamine-only strategy has been suggested as an alternative approach. Objective: We compared first attempt success and complications between ketamine-only, topical anesthesia alone or with low-dose sedation, and RSI approaches. Methods: We analyzed registry data from the National Emergency Airway Registry, comprising emergency department intubation data from 25 centers from January 2016 to December 2018. We excluded pediatric patients (<14 years of age), those in cardiac and respiratory arrest, or those with an alternate pharmacologic approach (i.e., neuromuscular blocking agent only or nonketamine sedative alone). We analyzed first attempt intubation success and adverse events across the 3 intubation approaches. We calculated differences in outcomes between the ketamine-only and topical anesthesia groups. Results: During the study period, 12,511 of 19,071 intubation encounters met inclusion criteria, including 102 (0.8%) intubated with ketamine alone, 80 (0.6%) who had intubation facilitated by topical anesthesia, and 12,329 (98.5%) who underwent RSI. Unadjusted first attempt success was 61%, 85%, and 90% for the 3 groups, respectively. Hypoxemia (defined as oxygen saturation <90%) occurred in 16%, 13%, and 8% of patients during the first attempt, respectively. At least 1 adverse event occurred in 32%, 19%, and 14% of the courses of intubation for the 3 groups, respectively. In comparing the ketamine-only and topical anesthesia groups, the difference in first pass success was −24% (95% confidence interval −37% to −12%), and the difference in number of cases with ≥1 adverse event was 13% (95% confidence interval 0–25%), both favoring the topical anesthesia group. Conclusion: Although sometimes advocated, the ketamine-only intubation approach is uncommon and is associated with lower success and higher complications compared with topical anesthesia and RSI approaches.**

☐ **Keywords—difficult airway; emergency intubation; ketamine; rapid sequence intubation; topical anesthesia**

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INTRODUCTION

Background

Tracheal intubation in the emergency department (ED) is most commonly accomplished using rapid sequence intubation (RSI), the near-simultaneous administration of a sedative agent and neuromuscular blocking agent (NMBA) (1). Among patients deemed not suitable for neuromuscular blockade, the intubating physician may select a variety of approaches. Most commonly, this patient population undergoes intubation with generous topical anesthesia of the upper airway and glottis, with minimal to no parenteral sedation (2). However, recently some have advocated for a "ketamine-only" approach to provide dissociative sedation with the goal to prevent aspiration and hypoxemia by preserving airway protective reflexes and spontaneous ventilation (3).

Neuromuscular blockade and RSI have improved the safety and success of emergency intubation compared with intubation facilitated by a sedative alone (4–7). However, the widespread adoption of video laryngoscopy, which may allow for less upper airway manipulation than traditional direct laryngoscopy, may make the ketamine-only approach safer than previously thought. Conversely, this approach could be less successful and have higher complications compared with RSI or other strategies (8). To our knowledge, the success and complications of the ketamine-only approach has not been studied in the ED.

Study Objective

We report first attempt intubation success and adverse events for patients who underwent intubation using ketamine-only, topical anesthesia, and RSI approaches.

MATERIALS AND METHODS

Study Design and Setting

We analyzed data from the National Emergency Airway Registry (NEAR), a registry of ED intubations collected from an international network of academic hospitals. Each participating site obtained approval from its local institutional review board to conduct the study.

Methods of Measurement and Data Collection and Processing

Detailed methods outlining data collection methods have been published previously (1,9). Intubating providers completed an online data collection instrument after each encounter to provide detailed information about the patient, intubation process, and outcomes (StudyTRAX v. 3.47.0011; ScienceTRAX, Macon, GA). The central coordinating center screens each entry for completeness and data consistencies. Each study site must complete data collection forms for ≥90% of intubations performed.

Selection of Participants

Of registry entries between January 1, 2016 and December 31, 2018, we included patients ≥14 years of age intubated orally or nasally using RSI (defined as administration of a sedative agent and NMBA), ketamine alone as a sedating agent without a NMBA, or topical anesthesia facilitation (defined as an intubation facilitated with topical anesthesia alone or in conjunction with sedative administration). We defined these 3 groups as the intubation strategies of interest. We excluded those with missing data for the primary outcome. We did not exclude patients with other missing data.

Outcome Measures

The primary outcome was successful intubation on the first attempt. For orotracheal intubation, we defined an attempt as a single insertion of the laryngoscope blade into the mouth. For nasal intubation, an attempt was defined as a single passage of a flexible endoscope with intent to intubate the trachea. Secondary outcomes included successful intubation on the first attempt for those with ≥1 difficult airway characteristics, successful intubation on the first attempt without any adverse events, the proportion of patients with Cormack–Lehane grade 1 or 2 on the first attempt, hypoxemia, adverse events during the first attempt, adverse events during the entire course of intubation, and whether an alteration in approach was made after a failed first attempt (including changing device, operator, or patient position; administering a NMBA, performing external laryngeal manipulation, or use of a bougie). Adverse events included cardiac arrest (defined as the receipt of cardiopulmonary resuscitation during or immediately after intubation), dental trauma, airway injury, esophageal intubation, hypoxemia (defined as an oxygen saturation by pulse oximetry of <90%), iatrogenic bleeding, epistaxis, hypotension, laryngospasm, medication error, laryngoscope failure, lip laceration, and pharyngeal laceration.

Primary Data Analysis

We present all analyses stratified by the study groups of interest: 1) patients intubated using ketamine only, without use of a NMBA, 2) patients intubated with use of topical anesthesia (including those who received

sedating medications with topical anesthesia), and 3) patients intubated using RSI. The intubation strategies of the first 2 groups maintain spontaneous breathing, which is usually reserved for patients deemed by the intubating physician to be higher than usual risk for a difficult intubation. The third group, RSI, is included as a reference group for usual emergency medicine airway management.

We describe baseline characteristics and intubation management, as well as unadjusted primary and secondary outcomes, all stratified by study group. It is important to account for differences in baseline characteristics and intubation management when analyzing retrospective data. However, the small numbers in the ketamine-only and topical anesthesia groups prevented a robust multivariate analysis; using the rule of tens, we could have only included 1 to 2 predictor variables (10). Therefore, we used descriptive techniques, presenting counts, percentages, medians, and interquartile ranges, and estimated absolute unadjusted differences in study outcomes between ketamine-only and topical anesthesia groups. We conducted all statistical analyses using Stata software (v. 15; StataCorp, College Station, TX).

RESULTS

Characteristics of Study Patients

Of 19,071 intubations in the NEAR registry during the study period, there were 12,511 eligible for analysis: 80 intubations using ketamine only, 102 intubations using topical anesthesia, and 12,329 intubations using RSI. Baseline characteristics and intubation management are displayed in Table 1. The median dose of intravenous ketamine in the ketamine-only group was 1.3 mg/kg (interquartile range 0.8–1.9 mg/kg). In the topical anesthesia group, 34 of 80 patients (43%) received intravenous ketamine to facilitate intubation, with a median dose of 0.6 mg/kg (interquartile range 0.3–1.3 mg/kg); 7 (9%) additional patients received etomidate or midazolam; the remainder received topical anesthesia alone.

Most patients in the ketamine-only and topical anesthesia groups had an initial impression of a difficult airway (75% and 90%, respectively), and had ≥1 difficult airway characteristic (72% and 80%, respectively). The intubation indication was angioedema and airway obstruction in 64% of encounters in the topical anesthesia group. Sedation for preoxygenation (sometimes termed delayed sequence intubation if a NMBA is later administered) was performed in 17% and 15% of the ketamine-only and topical anesthesia participants, respectively. While a video bronchoscope was used in the majority of topical anesthesia group patients (68%), a video laryngoscope was used most commonly in the ketamine-only group patients (59%). Video laryngoscope blade shapes by group are shown in Table 1.

Main Results

The primary outcome, successful intubation on the first attempt, was reported in 61% of patients in the ketamine-only group, 85% in the topical anesthesia group, and 90% in the RSI group (absolute difference between ketamine-only and topical anesthesia, −24% [95% confidence interval {CI} −37% to −12%], with topical anesthesia having higher success). Successful intubation on the first attempt without adverse events had similar magnitude of difference between groups (Table 2). In patients with an initial impression of a difficult airway, first attempt success was 41 of 77 (53%) for ketamine only, 60 of 72 (83%) for topical anesthesia, and 3158 of 3744 (84%) for RSI.

One or more adverse events occurred in 32% of ketamine-only intubations compared with 19% of intubations using topical anesthesia (absolute difference 13% [95% CI 0–25%]). After a failed first attempt, a NMBA was administered in the ketamine-only group in 23 of 40 patients (58%). The remaining changes after first attempt failure are shown in Table 2.

Limitations

There are several important limitations. First, because of small sample sizes we were unable to adjust for important confounders of the relationship between choice of pharmacologic strategy and intubation outcome, namely first attempt success and adverse events. The magnitude of the difference in these outcomes could be smaller if adjustment for other variables was performed. The small sample size, however, also speaks to the infrequency that physicians choose to use the ketamine-only approach preferentially over RSI. Second, some authors advocate for a specific approach when using ketamine-only which may improve its success and safety; granular data on procedural details and physician experience with a ketamine-only approach are lacking (3,11). It is possible that the outcomes would have differed among physicians experienced with this technique. Third, among patients who received topical anesthesia, 43% received ketamine to facilitate patient tolerance of intubation. We noted a 2-fold difference in the median dose of ketamine administered between these groups, which we interpret as evidence of 2 distinct airway management approaches. Fourth, it is probable that not all patients who underwent ketamine-only intubation were candidates for topical anesthesia or RSI approaches, so direct comparisons may be problematic. Therefore, differences in outcomes and adverse events between ketamine-only and topical

Table 1. Baseline Characteristics and Intubation Management

Variable	Ketamine Only, n = 102	Topical Anesthesia, n = 80	Rapid Sequence Intubation, n = 12,329
Baseline characteristics			
Mean age, years (SD)	54 (44–63)	59 (46–67)	53 (35–67)
Male, n (%)	68 (67)	53 (66)	8117 (66)
Obese/morbidly obese, n (%)	52 (51)	48 (60)	3762 (31)
Medical indication for intubation, n (%)	87 (86)	75 (94)	9206 (75)
Top 3 medical indications for intubation (%)			
First	Respiratory failure* (23)	Angioedema (33)	Nonoverdose mental status change (21)
Second	Nonoverdose mental status change (17)	Airway obstruction (31)	Overdose (13)
Third	Airway obstruction (16)	Respiratory failure* (18)	Respiratory failure* (13)
Initial impression of difficult airway, n (%)	77 (75)	72 (90)	3744 (30)
Any difficult airway characteristic,†n (%)	73 (72)	64 (80)	6197 (50)
Reduced neck mobility	24 (24)	16 (20)	3539 (29)
Reduced mouth opening	37 (36)	24 (30)	1806 (15)
Airway obstruction	24 (24)	53 (66)	411 (3)
Facial trauma	6 (6)	5 (6)	1421 (12)
Blood or vomit in airway	27 (26)	12 (15)	2720 (22)
Intubation management, n (%)			
Sedation required for preoxygenation‡	17 (17)	12 (15)	671 (5)
Flexible video bronchoscope used for first nasal or oral intubation attempt	19 (19)	64 (68)	42 (0.3)
Video laryngoscope used for first attempt	60 (59)	10 (13)	8610 (70)
Video laryngoscope blade shape			
Standard geometry, n/N (%)	27/60 (45)	1/10 (10)	5278/8610 (61)
Hyperangulated, n/N (%)	33/60 (55)	9/10 (90)	3332/8610 (39)
SpO_2 at attempt start, median (IQR)	99 (96–100)	100 (97–100)	100 (98–100)
SpO_2 <90% at attempt start	7 (7)	6 (8)	566 (5)
Intubator characteristics, n (%)			
EM PGY1	5 (5)	3 (4)	1393 (11)
EM PGY2	29 (28)	16 (20)	3695 (30)
EM PGY3–4	57 (56)	43 (54)	5917 (48)
EM fellow	1 (1)	6 (8)	352 (3)
EM attending physician	4 (4)	3 (4)	372 (3)
Other (non-EM)	6 (6)	9 (11)	600 (5)

EM = emergency medicine; IQR = interquartile ratio; PGY = postgraduate year; SpO_2 = oxygen saturation.
* Respiratory failure included the following indications: anaphylaxis, asthma, congestive heart failure, chronic obstructive pulmonary disease, pneumonia, and pulmonary embolism.
† Difficult airway characteristics coded as yes if the patient had ≥1 of the following: reduced neck mobility, Mallampati score >1, reduced mouth opening, airway obstruction, facial trauma, and blood or vomit in the airway.
‡ Sometimes known as "delayed sequence intubation" if followed by neuromuscular blockade.

Table 2. Outcomes

Outcome	Ketamine Only, n = 102	Topical Anesthesia, n = 80	Rapid Sequence Intubation, n = 12,329	Difference Between Ketamine and Topical (95% CI)*
Successful intubation on the first attempt, n (%)	62 (61)	68 (85)	11,094 (90)	−24% (−37% to −12%)
Successful intubation on the first attempt, in those with ≥1 DAC	37/73 (51)	55/64 (86)	5411/6197 (87)	−35% (−50% to −21%)
Successful intubation on the first attempt, without adverse events, n (%)	56 (55)	62 (78)	10,255 (83)	−23% (−36% to −9%)
Cormack–Lehane view grade 1–2, n (%)	78 (76)	60 (75)	10,950 (89)	1% (−11% to 14%)
Hypoxemia during first attempt, n (%)	16 (16)	10 (13)	992 (8)	3% (−7% to 13%)
Any adverse event during first attempt, n (%)	19 (19)	10 (13)†	1199 (10)	6% (−4% to 17%)
Selected adverse events for first attempt,‡n (%)				
Cardiac arrest	1 (1)	0	110 (1)	
Vomiting	7 (7)	0	73 (1)	NA
Esophageal intubation	1 (1)	0	71 (1)	NA
Epistaxis	1 (1)	0	4 (<1)	NA
Laryngospasm	2 (2)	0	7 (<1)	NA
Any adverse event during course of intubation	32 (32)	15 (19)	1726 (14)	13% (0–5%)
After failed first attempt, changes in management,§n (%)	N = 40	N = 12	N = 1235	−4% (−23% to 15%)
Add NMBA	23 (58)	5 (42)	N/A	
Change device	22 (56)	7 (58)	584 (48)	
Change intubator	6 (15)	4 (33)	112 (9)	
Change patient position	13 (33)	6 (50)	130 (11)	
Use ELM	5 (13)	3 (25)	91 (7)	
Use bougie	9 (23)	4 (33)	222 (18)	
Any change	35 (88)	11 (92)	858 (69)	

CI = confidence interval; DAC = difficult airway characteristic; ELM = external laryngeal manipulation; NA = not applicable; NMBA = neuromuscular blocking agent.
* This column shows the difference between ketamine-only and topical anesthesia approaches. Negative numbers correspond to a higher numerical value for topical anesthesia.
† Ten patients had hypoxemia, 2 had hypotension.
‡ Numbers too small to calculate estimated difference.
§ Some patients had >1 change, thus the total exceeds the number of failed first attempts.

anesthesia are preliminary estimates, and the RSI group was included for reference only, without estimating between-group differences. Fifth, observed differences between the ketamine-only and topical anesthesia groups may be partially related to differences in intubation technique (oral vs. nasal), rather than solely because of the pharmacology of each approach. However, endoscopic nasal techniques are easier when the patient can cooperate and follow prompts, which is not possible when ketamine causes dissociation. Sixth, most intubations were performed by residents in training. Although >50% of intubations were performed by residents in the third postgraduate year or higher, indicating probable substantial intubating experience, these results may not generalize to all emergency physicians.

DISCUSSION

In this registry analysis, we found that when the ketamine-only method was used to facilitate intubation, success was lower and adverse events were higher when compared with an approach facilitated primarily by topical anesthesia. While we could not control for important differences in groups because few ED patients underwent either technique, the success of the ketamine only approach was quite low (61%) compared with traditional ED intubation success (12).

To our knowledge, there are no previous rigorous analyses of the ketamine-only intubation approach in the ED. Although it is described as a reasonable option when a difficult airway is suspected, it appears that this technique is quite uncommon in academic emergency medicine practice, occurring in <1% of intubations in the NEAR registry. Descriptions of prehospital success of the ketamine-only approach are also limited, but 2 small studies, taken together, report first attempt intubation success in 21 of 31 patients (68%) with this technique, similar to the success rate seen in this study (13,14). Mosier et al. used propensity score matching to compare intubation outcomes in the intensive care unit with and without a NMBA, finding lower success when NMBAs were not used; in that study, ketamine was the most common medication given without a NMBA (5).

The ketamine-only technique is ostensibly used for patients with anticipated difficult intubation. For those with ≥1 difficult airway characteristic, however, success with ketamine only (51%) was far lower than with topical anesthesia (86%) or RSI (87%) in this population. Furthermore, first attempt success with ketamine only (51%) in the NEAR registry was lower than success rates reported in other studies for patients with difficult airway characteristics, which range from 78% to 90% (12,15). This is despite the fact that patients intubated with topical anesthesia facilitation had higher rates of anatomic distortion than those intubated with ketamine only. Patient selection may explain much of the difference between ketamine-only and topical anesthesia success; patients receiving ketamine only may have been unsuitable for topical anesthesia techniques because of excessive oral secretions or bleeding, inadequate cooperation, lack of equipment, or lack of experience with topical anesthesia application and endoscopic intubation.

It is unclear if the theoretical benefits of a ketamine-only approach outweigh the risks observed in the current study and how this approach compares with RSI when using a modern extraglottic device and cricothyrotomy as backup approaches. We do not know how patients would have fared if RSI was used instead, which provides full control of the patient, and has been shown in several studies and a systematic review to result in in better glottic views, higher success, and fewer complications compared with intubation with a sedative alone (4–7,16,17). In the current study, administration of a NMBA was the most common change for ketamine-only patients after the first attempt was unsuccessful.

Although RSI has been shown, in general, to be superior to withholding a NMBA, it is possible that the ketamine-only approach is the best approach in select circumstances, possibly including scenarios when NMBAs must absolutely be avoided and the physician does not have access to an endoscope or the skill to use it. However, the ideal circumstances for ketamine-only are speculative and not currently supported by empirical data. It may be prudent for emergency physicians to use widely accepted emergency airway management algorithms until data support the success and safety of the ketamine-only approach (2).

While ketamine usually preserves spontaneous breathing, there are case reports of apnea in critically ill patients and it frequently results in at least subclinical respiratory depression (18–20). This is an important consideration in patients with a severe metabolic acidosis because the goal is usually to preserve the compensatory high minute ventilation. It may be preferable to induce full muscle relaxation and apnea with neuromuscular blockade, facilitating a best attempt at intubation, rather than risk a longer, ketamine-facilitated intubation attempt with relative hypoventilation and lesser chance of success. In the ED, sedation-only intubation approaches can lead to a dangerous circumstance: respiratory depression without enough muscle relaxation to facilitate tube passage. Sedation-only approaches may have fallen out of favor in the era of RSI because they seem to lack the primary benefits of both the awake approach (optimal ability of patient to breath and protect their own airway) and RSI (optimal preoxygenation and laryngoscopy conditions). Vomiting, seen in 7% of patients with ketamine-only intubations, is another known complication of ketamine.

Although vomiting related to ketamine use in procedural sedation usually occurs late in the recovery phase when patients can clear their own airway, any vomiting caused by an intubation technique could lead to large-volume aspiration, a feared complication of emergency airway management (21).

CONCLUSION

Although the ketamine-only technique is sometimes advocated, it was rarely used in this large ED registry, and had lower success and a higher rate of adverse events than other airway management strategies.

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ARTICLE SUMMARY

1. Why is this topic important?

Some advocate for ketamine alone, without neuromuscular blockade, when a difficult intubation is anticipated. Previous data show that intubation without neuromuscular blockade has poorer outcomes.

2. What does this study attempt to show?

Do success and complications differ when ketamine is administered alone for intubation, at dissociative doses, compared with intubation facilitated by topical anesthesia alone or in conjunction with low-dose sedation?

3. What are the key findings?

We examined 12,511 intubation encounters, including 102 (0.8%) intubated with ketamine alone and 80 (0.6%) who had intubation facilitated by topical anesthesia. In comparing the ketamine-only and topical anesthesia groups, the difference in first pass success was −24% (95% confidence interval −37% to −12%), and the difference in number of cases with ≥1 adverse event was 13% (95% confidence interval 0–25%), both favoring the topical anesthesia group.

4. How is patient care impacted?

Although sometimes advocated, the ketamine-only intubation approach is uncommon and associated with lower success and higher complications compared with topical anesthesia and RSI approaches.