ORIGINAL CLINICAL RESEARCH REPORT

Peri-Intubation Hypoxia After Delayed Versus Rapid Sequence Intubation in Critically Injured Patients on Arrival to Trauma Triage: A Randomized Controlled Trial

Anjishnujit Bandyopadhyay, DM, Pankaj Kumar, MD, Anudeep Jafra, MD, Haneesh Thakur, MD, Laxmi Narayana Yaddanapudi, MD, and Kajal Jain, MD

BACKGROUND: Critically injured patients who are agitated and delirious on arrival do not allow optimal preoxygenation in the emergency area. We investigated whether the administration of intravenous (IV) ketamine 3 minutes before administration of a muscle relaxant is associated with better oxygen saturation levels while intubating these patients.

METHODS: Two hundred critically injured patients who required definitive airway management on arrival were recruited. The subjects were randomized as delayed sequence intubation (group DSI) or rapid sequence intubation (group RSI). In group DSI, patients received a dissociative dose of ketamine followed by 3 minutes of preoxygenation and paralysis using IV succinylcholine for intubation. In group RSI, a 3-minute preoxygenation was performed before induction and paralysis using the same drugs, as described conventionally. The primary outcome was incidence of peri-intubation hypoxia. Secondary outcomes were first-attempt success rate, use of adjuncts, airway injuries, and hemodynamic parameters.

RESULTS: Peri-intubation hypoxia was significantly lower in group DSI (8 [8%]) compared to group RSI (35 [35%]; *P* = .001). First-attempt success rate was higher in group DSI (83% vs 69%; *P* = .02). A significant improvement in mean oxygen saturation levels from baseline values was seen in group DSI only. There was no incidence of hemodynamic instability. There was no statistically significant difference in airway-related adverse events.

CONCLUSIONS: DSI appears promising in critically injured trauma patients who do not allow adequate preoxygenation due to agitation and delirium and require definitive airway on arrival. (Anesth Analg 2023;136:913–9)

KEY POINTS

- **Question:** Does delayed sequence intubation decrease peri-intubation hypoxia in trauma patients compared to rapid sequence intubation?
- **Findings:** Delayed sequence intubation significantly decreases peri-intubation hypoxia compared to rapid sequence intubation.
- **Meaning:** Delayed sequence intubation ensures adequate preoxygenation, thus decreasing hypoxia during intubation.

GLOSSARY

ATLS = advanced trauma life support; **BMV** = bag and mask ventilation; **CL** = Cormack-Lehane; CONSORT = Consolidated Standards of Reporting Trials; **CTRI** = Clinical Trials Registry of India; **DBP** = diastolic blood pressure; **DM** = diabetes mellitus; **DSI** = delayed sequence intubation; **GCS** = Glasgow Coma Scale; **HR** = heart rate; **HTN** = hypertension; **IEC** = institute ethics committee; **INTUBE** = International Observational Study to Understand the Impact and Best Practices of Airway Management in Critically Ill Patients; **IQR** = interquartile range; **IV** = intravenous; **MVA** = motor vehicle accident; **NIBP** = noninvasive blood pressure; **NMDA** = *N*-methyl-D-aspartate; **RCT** = randomized controlled trial; **RSI** = rapid sequence intubation; **SBP** = systolic blood pressure; **SD** = standard deviation; **TBI** = traumatic brain injury

From the Department of Anaesthesia and Intensive care, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

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Address correspondence to Kajal Jain, MD, Department of Anaesthesia and Intensive Care, Level 4, Nehru Hospital, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India. Address e-mail to kajalteji@gmail.com

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Securing definitive airway in trauma emergency is a daunting task due to trauma-induced factors, such as soiled airways and critical faciomaxillary, cervical spine, and head injuries.[1] Trauma patients are agitated and delirious due to pain, lower neurological status, and hypoxia. Therefore, the trauma airway places a physiological challenge to the airway manager. The recent Advanced Trauma Life Support (ATLS) guidelines suggest drug-assisted intubation in the trauma bay using anesthetic, sedative, and neuromuscular blocking drugs. Due to familiarity with the technique of rapid sequence intubation (RSI), many providers prefer this technique for emergency intubations.[2,3] During RSI, preoxygenation is followed by near-simultaneous administration of an induction agent and a rapid-acting neuromuscular blocker to facilitate intubation without ventilation in between. For patients with agitation or combativeness who do not tolerate standard preoxygenation, RSI can be modified with the addition of gentle positive pressure ventilation after induction and before intubation with a potential increase in the risk of gastric distension and aspiration. Despite these maneuvers, the goal of achieving adequate preoxygenation is often unmet, especially if the patient is agitated and delirious. A higher incidence of peri-intubation desaturation has been reported in the literature.[4,5] Peri-intubation hypoxia can hold significant implications in trauma patients, especially those with associated head injury. Hypoxia results in secondary injuries to an already compromised brain and leads to poorer outcomes. Other peri-intubation adverse events, like hemodynamic instability, direct airway trauma, and vomiting with or without pulmonary aspiration, have also been reported.[6]

Delayed sequence intubation (DSI) is a relatively new technique that utilizes a dissociative dose of ketamine, goal-directed preoxygenation for a minimum of 3 minutes, a neuromuscular blocker, and intubation. A ketamine-induced dissociative state helps in relieving agitation and pain, while maintaining spontaneous respiration and airway reflexes.[7] Data utilizing DSI have been studied in several observational trials during emergency airway management.[8–10] DSI may also be beneficial to other settings, especially trauma emergency, when securing the airway poses a significant challenge. This prospective randomized trial aimed to compare 2 different drug-assisted intubation techniques: RSI and DSI. The primary outcome was to note the incidence of peri-intubation hypoxia in critically injured patients requiring definitive airway management on arrival.

METHODS

This study was approved by the institute ethics committee (INT/IEC/2019/000326), and deferred written informed consent was obtained from all subjects participating in the trial. The trial was registered before patient enrollment at Clinical Trials Registry of India (CTRI/2019/05/019388, http://ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=32055&EncHid=&modid=&compid=%27,%2732055det%27; principal investigator: Pankaj Kumar, date of registration: May 27, 2019).

Adult trauma patients who presented to trauma emergency and required definitive airway with endotracheal intubation were assessed for enrollment in the study. Patients with anticipated difficult airway, extensive burns, active vomiting, crash intubations, or cardiac arrest were excluded from the study. All patients with unanticipated difficult airway encountered during the study were excluded from the primary analysis. Difficult airway was defined as any difficulty faced in one or more of the following: mask ventilation, laryngoscopy, and tracheal intubation.[11] All emergency airway management procedures are lifesaving, and hence, we obtained "deferred consent" from legal surrogates of enrolled subjects. An option of "opting out" was offered to the legal surrogate when deemed necessary.

Patients were randomly allocated in a 1:1 ratio to either group RSI or group DSI via computer-generated random number codes, which were kept concealed in sequentially numbered sealed opaque envelopes. The sealed opaque envelopes were opened up by the on-duty nursing officer before airway management. This nursing officer was not further involved in the study. All intubations were performed by a second-year postgraduate anesthesia resident who was a member of the airway response team. Another anesthesiologist administered the drug sequence as per random number and also kept a record of the data on a standardized proforma (Supplemental Digital Content 1, Data File 1, http://links.lww.com/AA/E26). Due to inherent problems with blinding in the emergency area, the intubator and the anesthesiologist injecting drugs were not blinded to group allocation. However, patients and the data analyzer were blinded to the group allocation. The intubation procedure as per randomization was as follows:

1. Group RSI: preoxygenation for 3 minutes followed by induction with intravenous (IV) ketamine 1.5 mg/kg and IV succinylcholine 1.5 mg/kg followed by endotracheal intubation.
2. Group DSI: IV ketamine 1.5 mg/kg in 0.5-mg/kg increments until dissociation was achieved (patient is calm but spontaneously breathing) followed by preoxygenation for 3 minutes followed by IV succinylcholine 1.5 mg/kg and endotracheal intubation.

Patients were preoxygenated via spontaneous tidal breathing for 3 minutes using a facemask attached to a Bain circuit, with oxygen at 10 liters per minute.

Intubation was performed using direct laryngoscopy in both groups. An intubation attempt was defined as any insertion of laryngoscope beyond teeth irrespective of intubation success. An attempt was considered successful after confirmation by bilateral chest auscultation, adequate chest rise, and mist in endotracheal tube. The detailed proforma included patient's history, airway characteristics, indications, hemodynamic parameters such as heart rate (HR) and noninvasive blood pressure (NIBP), and pulse oximetry recorded at baseline (0 minutes), at each 1-minute interval for 3 minutes during preoxygenation, and 1 minute after intubation. The primary outcome was incidence of peri-intubation hypoxia defined as an oxygen saturation of Spo_2 <93% anytime from preoxygenation until 1 minute after intubation. Hypotension was considered if systolic blood pressure (SBP) was <100 mm Hg, and bradycardia was considered when HR was <60/min. Secondary objectives included hemodynamic data at predefined intervals of intubation, Cormack-Lehane (CL) grading, first-attempt success rate, use of airway adjuncts, incidence of airway injuries, and cardiac arrest.

Statistical Analysis

Data were analyzed using SPSS version 22.0. The incidence of peri-intubation hypoxia has been reported to be around 57% in trauma patients.[12] Assuming a 20% absolute reduction in incidence of peri-intubation hypoxia in group DSI compared to group RSI, with a 2-sided α of <0.05 and a β error of 0.2, 97 patients were required for each group. Sample size and power calculation were done using 2-sample Z test of proportions. We included 100 patients in each group to account for dropouts. The comparison of variables between 2 groups (RSI versus DSI) was performed using the Student *t* test or Mann-Whitney *U* test for quantitative parametric and nonparametric data, respectively. Normality of data was checked using the Kolmogorov-Smirnov test. Categorical variables were analyzed using the χ^2 test or Fisher exact test wherever applicable. A multivariable logistic regression model was used to calculate adjusted odds ratios for factors that could potentially influence the primary outcome.

RESULTS

The CONSORT diagram depicting flow of patients is shown in Figure 1. A larger sample than our calculated sample size (n = 200) was randomized, as unanticipated difficult airways encountered were set aside as per exclusion criteria.

The demographic data are presented in Table 1. The most common indication for intubation was altered mental status due to polytrauma with associated head injury (DSI, 95/100; RSI, 100/100) and respiratory distress (DSI, 5/100; RSI, 0/100). The median value of the Glasgow Coma Scale (GCS) in both groups was comparable (group DSI, 6 [IQR, 4–7] vs group RSI, 6 [IQR, 4–7]; *P* = .827).

We recorded oxygen saturation values at baseline, then every 1 minute for 3 minutes during the period of preoxygenation and thereafter 1 minute after intubation. The primary outcome (ie, incidence of peri-intubation hypoxia) was significantly higher in group RSI (35 [35%]) than in group DSI (8 [8%]; *P* = <.001*; Table 2). The median Spo_2 values were significantly higher in group DSI compared to group RSI at all time points, except at baseline, where Spo_2 values were higher in group RSI (Table 2; Figure 2). There was no statistically significant difference in the hemodynamic parameters measured at predefined time intervals in both groups (Table 3).

The first-pass intubation success rate was significantly higher in group DSI compared to group RSI (*P* = .020); 83% of patients in group DSI and 69% patients in group RSI were intubated on the first attempt. Of the 17 patients in group DSI who could not be intubated on the first attempt, 8 were due to desaturation, which mandated bag and mask ventilation (BMV), 4 needed a change of blade, and 5 patients needed blade repositioning. In group RSI, of 35 patients who desaturated, 31 needed rescue BMV, but 4 patients were successfully intubated within seconds of desaturation, and a second attempt was not needed. CL grades were comparable between the 2 groups (Table 4).

Airway-related adverse events were also comparable in both groups (9% vs 16% in groups DSI and RSI, respectively; *P* = .134). Fewer airway injuries were reported with successful first attempts (8.5% [13/152 of 200 patients]); whereas multiple attempts correlated with a higher percentage of airway injuries, which was statistically significant (31.2% [15/48 of 200 patients]; *P* = <.001). There were no reported episodes of hypotension, arrhythmias, or cardiac arrest in our study. A multivariate analysis revealed technique of intubation (DSI versus RSI) to be a significant predictor of peri-intubation hypoxia (adjusted odds ratio, 6.82 [2.82–16.48]; *P* = .001) among all other factors (Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/E27).

DISCUSSION

Definitive airway management with endotracheal intubation is deemed urgent on arrival to trauma triage.[13] Delays during tracheal intubation and multiple attempts at laryngoscopy are associated with a myriad of complications such as peri-intubation hypoxia, hypotension, arrhythmias, cardiac arrest, and death.[14–16] Hence, critically injured patients and their airway management in such an environment can make anatomically normal airways physiologically challenging.

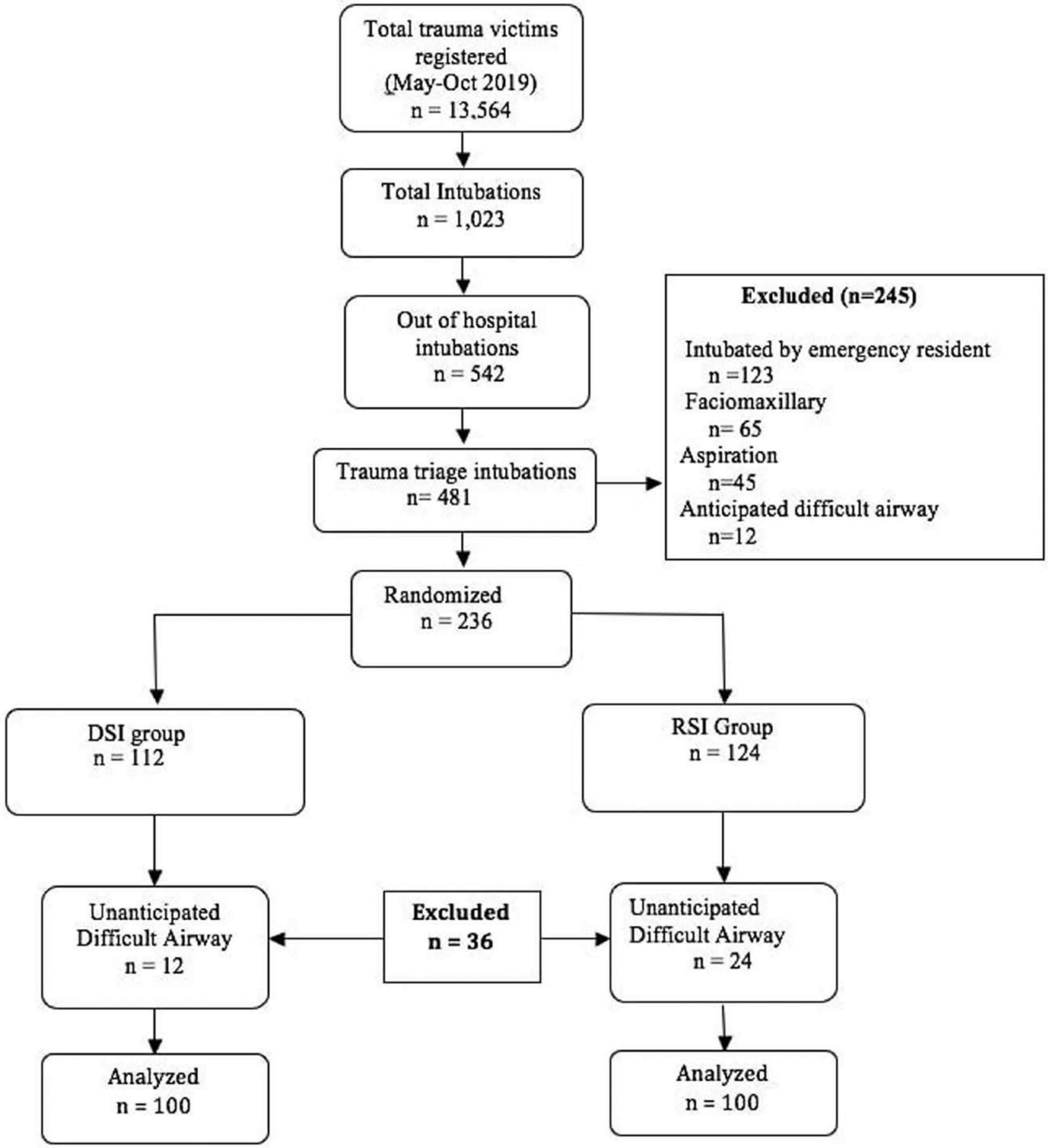

Figure 1. CONSORT diagram depicting flow of patients. CONSORT indicates Consolidated Standards of Reporting Trials; DSI, delayed sequence intubation, RSI, rapid sequence intubation.

In our cohort of patients, 97.5% were intubated in view of low GCS as a result of head injury. In concordance with previous data from emergency settings, our baseline data also depicted lower trends of oxygen saturation, indicating hypoxia on arrival. Any further episode of hypoxia, such as that occurring during intubation, can enhance secondary insults and morbidity.[17] Certain interventions that help reduce the risk of desaturation before intubation include denitrogenation, upright position, mask ventilation, high-flow nasal oxygen, and use of nonrebreathing bag.[18] Preoxygenation allows denitrogenation and increases the oxygen content of functional reserve capacity, thus creating an intrapulmonary reservoir of oxygen that prevents hypoxemia during the apneic phase of intubation. However, there are studies reporting desaturation despite this maneuver. Bodily et al reported the incidence of oxygen

Table 1. Demographic Characteristics

	Groups	
Characteristic	**DSI (n = 100)**	**RSI (n = 100)**
Age, y[a]	38.5 ± 14.9[a] (18–76)	39.3 ± 16.3[a] (18–80)
Male/female	84/16	91/9
GCS[b]	6.0 (4.0–7.7)	6.0 (4–7)
Mode of injuries[c]		
MVA	82	82
Fall from height	14	15
Closed head injury	4	2
Unknown mechanism	0	1
Indications of intubation[c]		
Poor GCS	95	100
Respiratory distress	5	0
Comorbidities[c]		
None	89	86
DM	6	2
HTN	2	7
Hypothyroid	2	0
DM + HTN	1	3

Data are presented as
[a]mean ± SD,
[b]median (IQR), and
[c]number of patients (percentage).
Abbreviations: DM, diabetes mellitus; DSI, delayed sequence intubation; GCS, Glasgow Coma Scale; HTN, hypertension; IQR, interquartile range; MVA, motor vehicle accident; RSI, rapid sequence intubation; SD, standard deviation.

Table 2. Oxygen Saturation at Various Time Points and Incidence of Peri-Intubation Hypoxia

Time (minutes)	Group DSI (n = 100)	Group RSI (n = 100)	*P* value
Baseline[a]	91 (88.5–95)	92 (90–96)	.04
1[a]	99 (98–100)	99 (90–99)	<.001
2[a]	100 (99–100)	99 (96–100)	.001
3[a]	100 (100–100)	100 (99–100)	.014
1 min after intubation[a]	100 (100–100)	100 (99–100)	.012
Incidence of peri-intubation hypoxia[b]	8%	35%	.00

[a]Data are presented as median (IQR); *P* value <.05 significant; Mann-Whitney *U* test.
[b]Data are represented as percentage; *P* value <.05 significant; χ^2 test.
Abbreviations: DSI, delayed sequence intubation; IQR, interquartile range; RSI, rapid sequence intubation.

desaturation to be 35.5% in spite of preoxygenation during RSI in the emergency department.[5] Similarly, Dunford et al[12] reported that 31 of 54 (57%) patients experienced desaturation after RSI protocol. Similar to these previous data, we also observed a higher incidence of peri-intubation hypoxia (ie, 35% after RSI). However, the incidence was lower (8%) when DSI, an alternate drug-assisted technique, was utilized in our study. Trauma patients show agitation and delirium due to various reasons like pain, hypoxia, or lower levels of consciousness. These patients do not cooperate for facemask application and, hence, are not adequately preoxygenated. Repeated attempts to restore oxygen saturation using BMV causes an increase in airway-related adverse events, notably aspiration.[7]As another technique, DSI employs an alternative drug sequence during which preoxygenation is done after administering a dissociative dose of ketamine. Weingart et al[8] reported an improved saturation from a mean of 89.9% to 98.8% after DSI (95% confidence interval, 6.4–10.9). This observational study included a mixed patient population (medical and trauma) that was deemed to have failed preoxygenation due to delirium. Our study sample was taken from another emergency setting consisting of critically injured trauma patients of whom the majority were obtunded, agitated, or delirious. We also observed similar results as those stated by Weingart et al.[8] Pain is perhaps an important cause of agitation and delirium after trauma. Ketamine relieves pain and decreases agitation and delirium, allowing for better acceptance of mask for preoxygenation compared to group RSI.

We report a higher first-pass success rate for group DSI compared to group RSI. Interruptions for performing rescue BMV in view of desaturation to achieve targeted saturation levels resulted in an increased number of attempts. RSI has been associated with a higher first-attempt success rate, as reported in previous studies.[18] Since our study was also not adequately powered to detect this difference, our findings need to be substantiated in future studies. Many factors, such as operator experience, patient-related factors, advanced equipment such as video laryngoscope, or bougie, if used, increase first-pass success rates.[4]

In our study, of the total 152 first-pass intubations, 9.3% patients sustained minor airway injuries, including lip injuries or bleeding. Intubations in the emergency room pose a significant challenge. It has been well reported that repeated attempts led to an increased incidence (31.2%) of airway injuries[15,19] Our results are also in coherence with the INTUBE study (International Observational Study to Understand the Impact and Best Practices of Airway Management in Critically Ill Patients), in which it is emphasized that drug-assisted techniques facilitate higher first-pass intubation success.[20]

A number of induction drugs like midazolam, propofol, thiopentone, and etomidate have been used in trauma intubations. Some of these drugs can cause apnea, hypotension, and tachycardia.[21] Wafaisade et al[22] demonstrated that ketamine does not appear to be inferior to other drugs for providing optimal intubating conditions. A recently concluded single-center randomized controlled trial (RCT) on emergency intubations comparing etomidate and ketamine reported significantly lower 7-day mortality with ketamine.[23] Ketamine has been suggested as an appropriate anesthetic drug for RSI in trauma victims because of its catecholamine-mediated stabilizing effect on the cardiovascular system.[24] Our results are in agreement with previous reports on hemodynamic profile after ketamine use. The use of ketamine, along with a fluid bolus,

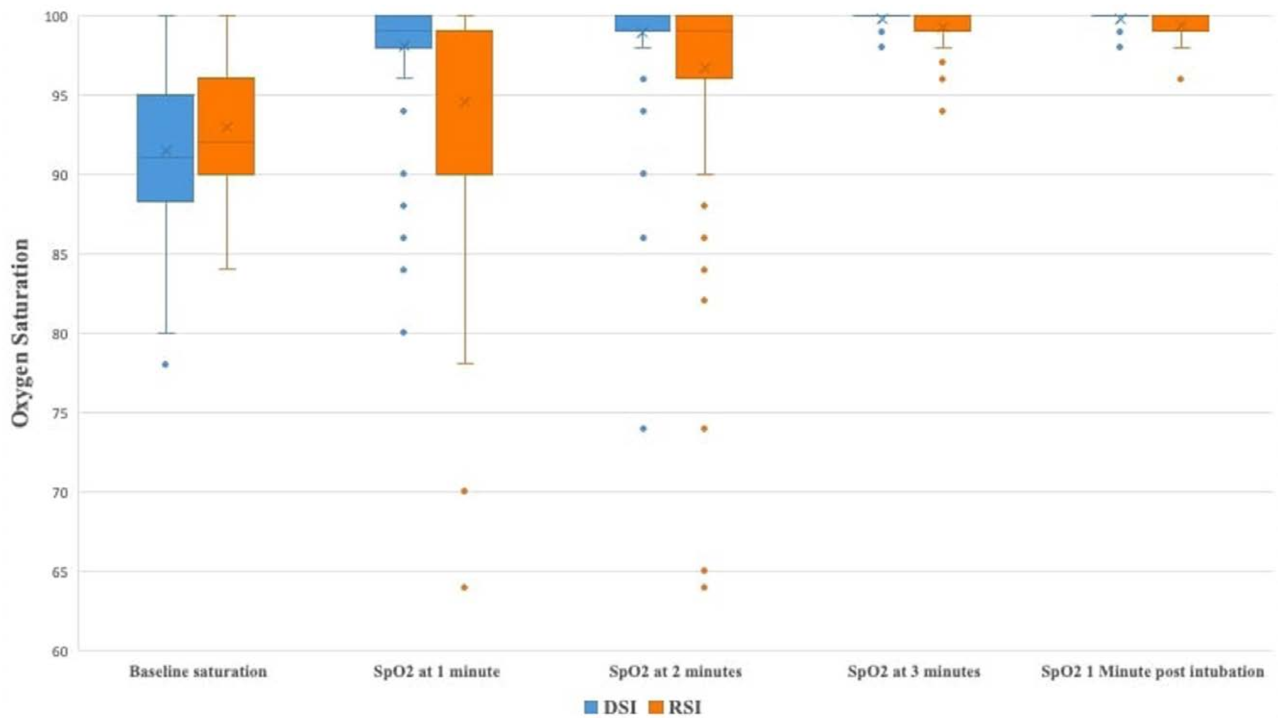

Figure 2. Box and whiskers plot depicting oxygen saturation at various time points in DSI versus RSI groups. DSI indicates delayed sequence intubation, RSI, rapid sequence intubation; Spo_2, oxygen saturation.

Table 3. Peri-Intubation Hemodynamic Data

	SBP			DBP			HR		
Time	DSI	RSI	*P* value	DSI	RSI	*P* value	DSI	RSI	*P* value
Baseline	100 (94–114)	100 (90–115.5)	.782	56 (50–64)	56 (48–64.5)	.370	93 (79–100)	87 (78–98)	.309
1	114 (101–122)	112 (101–124)	.823	58 (52–66)	58 (50–65.5)	.675	97 (84–105)	88 (83–99)	.262
2	116 (108–124)	114 (104–126)	.691	60 (54–68)	60 (52–68)	.244	98 (84–108)	91.5 (84–99)	.194
3	118 (112–128)	118 (109–130)	.913	60 (56–68)	61 (54–68)	.918	98 (86–108)	93.5 (85–102)	.120
1 min after intubation	124 (116–128)	118 (114–131)	.820	63 (57–72)	62 (56–69)	.582	94 (84–104)	93 (83.5–98)	.094

Data are presented as median (IQR); *P* value >.05 not significant; Mann-Whitney *U* test.
Abbreviations: DBP, diastolic blood pressure; DSI, delayed sequence intubation; HR, heart rate; IQR, interquartile range; RSI, rapid sequence intubation; SBP, systolic blood pressure.

Table 4. Secondary Outcomes

Outcome		Group DSI (n = 100)	RSI group (n = 100)	*P* value
First-attempt success rates		83%	69%	.02
CL grades				
I	49%	51%		
II	51%	45%		
III	2%	4%		
Airway injuries		9%	16%	.13
Use of airway adjuncts		31%	39%	.29

Data are presented as percentages; *P* value <.05 significant; χ^2 test.
Abbreviations: CL, Cormack-Lehane; DSI, delayed sequence intubation; RSI, rapid sequence intubation.

provided hemodynamic stability during intubation. The role of ketamine in head-injured patients is controversial, as it is known to increase cerebral blood flow, oxygen consumption, and, hence, an increase in intracranial pressure. However, recent literature cites the neuroprotectant effect of ketamine due to its ability to antagonize *N*-methyl-D-aspartate (NMDA) receptors.[25] Ketamine remains a favorable choice in trauma patients with traumatic brain injury (TBI), with a potential for cardiovascular stability as well.[23,26]

To the best of our knowledge, this is the first randomized trial comparing DSI and RSI in critically injured patients requiring intubation on arrival to trauma triage. Despite the strengths, there are some limitations of this study. The study was conducted on patients with structurally normal airways. In real-world scenarios, trauma intubations are threatened with soiled, aspirated airways, unanticipated or known difficult airways, and shock. Drug-assisted intubations utilizing DSI in these indications would be intriguing to study further. We were not able to measure end-tidal oxygen as a target end point of preoxygenation or use end-tidal carbon dioxide for confirmation of correct endotracheal tube placement. The intubating and record keeping anesthesiologist were unblinded to group allocation, and despite the fact that they were not involved in the study, investigator bias cannot be ruled out. In addition, all intubating anesthesiologists were still in training, and hence, results could be different for experienced physicians. Baseline agitation was also not quantified in our study.

To conclude, our prospective randomized study suggests that DSI reduces the incidence of peri-intubation hypoxia compared to RSI in trauma patients. Hence, it appears to be safe and effective in critically injured patients requiring definitive airway control on arrival.

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DISCLOSURES

Name: Anjishnujit Bandyopadhyay, DM.
Contribution: This author helped with data interpretation and analysis, literature search, writing the original draft, critical review of the manuscript, and manuscript approval.
Name: Pankaj Kumar, MD.
Contribution: This author helped with study design, data acquisition, and final approval of the manuscript.
Name: Anudeep Jafra, MD.
Contribution: This author helped with study design, critical review, and final approval of the manuscript.
Name: Haneesh Thakur, MD.
Contribution: This author helped with critical review and final approval of the manuscript.
Name: Laxmi Narayana Yaddanapudi, MD.
Contribution: This author helped with data analysis and final approval of the manuscript.
Name: Kajal Jain, MD.
Contribution: This author helped with design and supervision of the study, data interpretation, literature search, critical review, and final approval of the manuscript.
This manuscript was handled by: Richard P. Dutton, MD.

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