

Hindman BJ, Dexter F: Anesthetic Management of Emergency Endovascular Thrombectomy for Acute Ischemic Stroke. Part 2: Integrating and Applying Observational Reports and Randomized Clinical Trials

SUPPLEMENTAL DIGITAL CONTENT-2

OBSERVATIONAL REPORTS COMPARING SEDATION AND GENERAL ANESTHESIA FOR ENDOVASCULAR THROMBECTOMY:

BIAS INTRODUCED BY INCLUSION OF PATIENTS INTUBATED PRIOR TO ENDOVASCULAR THROMBECTOMY IN THE GENERAL ANESTHESIA GROUP

Many observational reports comparing sedation and general anesthesia (GA) considered all patients who were intubated before or during endovascular thrombectomy (EVT) to have received GA. Although this generalization may very often be true, it is not always. A patient may be intubated but not receive GA. A patient may receive GA but not be intubated. In addition, and very importantly, a patient may be intubated for reasons other than the need for GA. Observations from the IMS-III trial of patients who required intubation prior to EVT provide a quantitative demonstration of the effect of selection bias in observational reports.

In the IMS-III trial, 17/213 (8.0%) of the control group stroke patients (receiving tissue plasminogen activator [tPA] only, no EVT) were intubated within the first 7 hours of their care.¹ The indications for intubation were “concern for ability to protect airway/aspiration risk, cardiopulmonary deterioration, signs of herniation/increased intracranial pressure, inadequate pain control or agitation.” As shown in Table S2-1, compared to non-intubated stroke patients, stroke patients who were intubated had: 1) greater NIHSS scores; 2) a lesser incidence of good functional outcome (84/196 [43%] vs. 0/17 [0%], respectively; $P=0.0002$); and 3) greater hospital mortality (27/196 [14%] vs. 7/17 [41%], respectively; $P=0.0086$).¹ This mortality rate (41%) is consistent with other reports in which 11-12% of ischemic stroke patients (not undergoing EVT) were intubated and had a mortality rate of 40-70%.^{2,3} Therefore, in patients with acute ischemic stroke—*irrespective of EVT*—the need for intubation is a marker of stroke severity and/or co-morbidities that adversely affect outcome. The extent to which intubation independently contributes to less favorable outcomes in stroke patients (e.g., from ventilator-associated pneumonia) is not known.

Table S2-1. Risk Factors and Outcomes of Control Stroke Patients Who Were Intubated Within First Seven Hours of Presentation in the IMS-III Trial

IMS-III Trial Stroke Control Patients (tPA only) (n=213)	Not Intubated (n=196)	Medically Indicated Intubation (n=17)	P Value
Presentation NIHSS score	16 (8-30)	21 (10-30)	NR
3 month good outcome	84/196 (43%)	0/17 (0%)	<u>0.0002</u>
Hospital mortality	27/196 (14%)	7/17 (41%)	<u>0.0086</u>

Data abstracted from Abou-Chebl et al, 2015.¹ Values are median (25th-75th interquartile range) or incidence (percent). Underlined P values indicate values were calculated by the authors based on information provided in the original publication using Fisher’s exact test.

Abbreviations: NIHSS, National Institutes of Health Stroke Scale Score; NR, not reported in original publication; tPA, tissue plasminogen activator.

In this same trial (IMS-III), 434 patients were randomized to receive EVT. As summarized in Table S2-2, if they were not intubated, EVT patients were considered to have

received “sedation” (n=269). EVT patients were assumed to have received general anesthesia (“GA”, n=147) if they underwent endotracheal intubation within 7 hours of stroke onset, which was *assumed* to have occurred either before or during EVT. Compared with patients selected for sedation, patients selected for GA had several risk factors associated with less favorable EVT outcome: 1) greater NIHSS scores ($P<0.0001$); 2) a greater incidence of intracranial ICA occlusion ($P=0.06$); and 3) lesser (i.e., unfavorable) ASPECTS ($P=0.04$).¹ Accordingly, and not unexpectedly, when compared to patients selected to receive sedation, patients selected to receive GA (n=147) appeared to have less favorable 3-month functional status (relative risk=0.64; 95% CI=0.49-0.84; $P=0.0013$) and greater hospital mortality (relative risk=3.31, 95% CI=1.86-5.20; $P<0.0001$).

However, importantly, in “GA” patients, the indication for intubation was classified as either “routine practice” (elective intubation before EVT solely for GA [n=76]), or “medically indicated” (airway protection, cardiopulmonary deterioration, intracranial hypertension, [n=71]); see Table S2-2. Thus, in IMS-III, “medically indicated” intubation prior to EVT occurred in 71/416 (17%) of all EVT patients, and occurred in 71/147 (48%) of all patients selected for GA. None (0/269) of the sedation patients had pre-EVT intubation. As shown in Table S2-2, when compared to patients selected for sedation, the electively intubated patients did not have significantly less favorable 3-month neurologic outcome ($P=0.12$) or mortality ($P=0.11$). More striking and more telling, when compared to electively intubated patients, patients who had been intubated for “medical indications” had significantly greater hospital mortality ($P=0.027$). Thus, in IMS-III, the *apparent* adverse effect of “GA” (all GA patients, n=147) was probably due to the patients who had been intubated prior to EVT for “medical indications.” This study likely demonstrates an effect of selection bias.

Table S2-2. Risk Factors and Outcomes of EVT Patients as a Function of Intubation in the IMS-III Trial

IMS-III Trial EVT Patients (n=434)	“Sedation”	“General Anesthesia” (n=147)		Elective Intubation vs. Not Intubated (reference) RR (95% CI);^a P Value	Medically Indicated Intubation vs. Elective Intubation (reference) RR (95% CI);^a P Value
	Not Intubated (n=269)	Elective Intubation, (n=76)	Medically Indicated Intubation (n=71)		
Presentation NIHSS score	16 (7-29)	16 (7-40)	20 (11-40)	NR	NR
ASPECTS	8 (0-10)	8 (0-10)	7 (0-10)	NR	NR
ICA occlusion ^b	33/186 (18%)	19/66 (29%)	15/62 (24%)	NR	NR
3 month good outcome	129/269 (48%)	31/76 (41%)	14/71 (20%)	0.80 (0.60-1.06); P=0.12	0.62 (0.36-1.07); P=0.084
Hospital mortality	20/269 (7%)	10/76 (13%)	24/71 (34%)	1.82 (0.87-3.77); P= 0.11	2.16 (1.09-4.2); P=0.027

Data abstracted from Abou-Chebl et al, 2015.¹ Values are median (25th-75th interquartile range) or incidence (percent). P values are reported in the original publication.

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; EVT, endovascular thrombectomy; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale Score; NR, not reported in original publication; RR, relative risk.

a. Relative Risk adjusted for NIHSS score, age, and time to arterial puncture.

b. Not all patients had angiographic confirmation of occlusion location.

The frequency and indications for pre-EVT intubation in 24 observational reports comparing outcomes between sedation and GA are summarized in Table S2-3. Patients who were intubated prior to EVT were exclusively assigned to the GA group in 13 reports.^{1,4-6, 8,9,12-16,23,24} In 8 reports, pre-EVT intubation was not reported nor can it be inferred.^{10,17-19,21,22,25,26} In 2 reports, patients who were intubated prior to EVT were excluded from analysis.^{7,20} In only 1 report were patients who had been intubated prior to EVT included in both sedation and GA groups.¹¹ In the 7 reports that: 1) included patients who had pre-EVT intubation in their sedation vs. GA analysis; and 2) specifically reported the incidence of pre-EVT intubation,^{1,5,11,13,14,16,23} the incidence of pre-EVT intubation in patients selected for GA ranged between 9-100%, with an overall average of 148/602 (25%). In contrast, in these same 7 reports, the incidence of pre-EVT intubation in patients selected for sedation was 0% in 6 reports,^{1,5,13,14,16,23} and 12% in one report,¹¹ with an overall average of 9/904 (1%). Thus, in these 7 observational reports, it is *certain* that bias against GA was present because of the 25-fold greater incidence of pre-EVT intubation in patients selected for GA. It is also *certain* bias against GA was present in at least 7 other observational reports in which patients intubated *prior* to EVT were exclusively assigned to the GA group, but the incidence of pre-EVT intubation was not reported.^{4,6,8,9,12,15,24} This bias against GA may be present in at least some of the 8 observational reports in which pre-EVT intubation status was not reported nor can be inferred.^{10,17-19,21,22,25,26}

Table S2-3. Observational Reports Comparing Sedation and General Anesthesia for EVT: Pre-EVT Intubation

Observational Report, Reference	Pre-EVT Intubation in Entire Population	Indication for Pre-EVT Intubation	Patients Intubated Prior To EVT Included In Sedation group	Patients Intubated Prior To EVT Included In GA group
Nichols et al., 2010 ⁴	NR	NA	No ^a	Yes ^a
Sugg et al., 2010 ⁵	9/66 (14%)	Respiratory compromise before arrival to hospital or in emergency room	No, 0/57 (0%)	Yes, 9/9 (100%)
Abou-Chebl et al., 2010 ⁶	NR	NA	No ^a	Yes ^a
Jumaa et al., 2010 ⁷	30/264 (11%) ^b	Obtundation, airway protection, emesis	No, 0/73 (0%)	No, 0/53 (0%)
Davis et al., 2012 ⁸	NR	17/96 (18%) had airway obstruction, difficult intubation, decreased level of consciousness, aspiration prior to procedure	No ^a	Yes ^a
Hassan et al., 2012 ⁹	NR	NA	No ^a	Yes ^a
Langer et al., 2013 ¹⁰	NR	NA	Can't determine	Can't determine
Li et al., 2014 ¹¹	24/109 (22%)	Airway protection	Yes, 9/74 (12%)	Yes, 15/35 (43%)
John et al., 2014 ¹²	NR	Protection of airway from aspiration, agitation or combativeness, and decreased level of consciousness (Glasgow coma scale <8)	No ^a	Yes ^a
Whalin et al., 2014 ¹³	15/216 (7%)	NR	No, 0/83 (0%)	Yes, 15/133 (11%)
Abou-Chebl et al., 2014 ¹⁴	16/281 (6%)	Emergency intubation unrelated to EVT, otherwise NR	No, 0/82 (0%)	Yes, 16/170 (9%)
Abou-Chebl et al., 2015 ¹	71/416 (17%)	Protect airway/aspiration risk, cardiopulmonary deterioration, herniation/increased intracranial pressure, inadequate pain control or agitation	No, 0/269 (0%)	Yes, 71/147 (48%)
McDonald et al., 2015 ¹⁵	NR	NA	No ^a	Yes ^a
van den Berg et al., 2015 ¹⁶	7/348 (2%)	Agitation, respiratory insufficiency, decreased consciousness before EVT	No, 0/278 (0%)	Yes, 7/70 (10%)
Mundiyanapurath et al., 2015 ¹⁷	NR	NA	Can't determine	Can't determine
Sivasankar et al., 2016 ¹⁸	NR	NA	Can't determine	Can't determine
Just et al., 2016 ¹⁹	NR	NA	Can't determine	Can't determine
Janssen et al., 2016 ²⁰	4/88 (5%) ^b	NR	No, 0/31 (0%)	No, 0/53 (0%)
Berkhemer et al., 2016 ²¹	NR	NA	Can't determine	Can't determine
Bracard et al., 2016 ²²	NR	NA	Can't determine	Can't determine
Jagani et al., 2016 ²³	15/99 (15%)	NR	No, 0/61 (0%)	Yes, 15/38 (39%)
Bekelis et al., 2017 ²⁴	NR	NA	No ^a	Yes ^a
Slezak et al., 2017 ²⁵	NR	NA	Can't determine	Can't determine
Campbell et al., 2018 ²⁶	NR	NA	Can't determine	Can't determine

Abbreviations: EVT, endovascular thrombectomy; GA, general anesthesia; NA, not applicable; NR, not reported in original publication.

- a. Not formally stated, but inferred on the basis of reported methods.
- b. All patients intubated prior to EVT were excluded from sedation vs. GA analysis.

Supplemental Digital Content-2, References

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