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

SUPPPLEMENTAL DIGITAL CONTENT-3

OBSERVATIONAL REPORTS COMPARING SEDATION AND GENERAL ANESTHESIA FOR ENDOVASCULAR THROMBECTOMY:

HYPOTHESES REGARDING ANESTHESIA MANAGEMENT OF ENDOVASCULAR THROMBECTOMY

At the time this review was written (literature review, April, 2018), there were at least 24 observational reports comparing sedation and general anesthesia (GA) for endovascular thrombectomy (EVT). Most of these reports have identifiable biases against GA. Consequently, the "raw" (unadjusted) findings of most of these studies cannot be accepted at face value. On the other hand, neither can observational reports simply be dismissed or ignored. Observational studies allow for hypothesis *generation*. Such hypotheses guide the design of randomized clinical trials and the hypotheses that are formally tested.

Hypothesis #1: GA Increases the Time between the Decision for EVT and Achieving Reperfusion by About 20 Minutes

The benefit of EVT depends on minimizing the time between stroke onset and reperfusion. Accordingly, it has been asserted that sedation is preferable to GA because GA delays the start of EVT. Because providing GA absolutely requires an anesthesia team, but providing sedation does not, operationally, workflow delays associated with GA could have occurred because of one or more of following reasons: 1) an anesthesia-supported interventional suite was not immediately available; 2) an anesthesia team was not immediately available to travel to a remote interventional suite; 3) the anesthesia team was not included in routine EVT care and participated only when sedation failed; and/or 4) induction of GA and airway management requires more time than to start sedation.

As summarized in Table S3-1, observational reports suggest GA is often associated with ~20 minute delay between the time of hospital arrival and the start of EVT. However, after arrival in the interventional suite, there appears to be little delay associated with GA. In the only observational report to specifically report it, GA appeared to add an average of ~4 minutes to the time between the start of anesthesia and arterial puncture.[24] After arterial puncture, in some observational reports, GA appeared to be associated with less time to accomplish EVT. This may be because of the motion-free conditions of GA. Overall, in observational reports, the time between symptom onset and reperfusion is not consistently affected by method of anesthesia.[5, 14,22-24]

In observational reports, the delay associated with GA appears to be largely "up front," getting the patient, the interventional team, and anesthesia team together. More likely than not, this process varies among institutions and with the familiarity and effectiveness of the various teams. In the ESCAPE trial, use of GA for EVT was "actively discouraged" (Dr. Manyank Goyal, Department of Radiology, University of Calgary, Canada, personal communication, May 7, 2018). Accordingly, in the ESCAPE trial, only 9% of patients received GA for EVT. In ESCAPE: 1) mean time between CT scan and groin puncture was ~22 min greater in GA patients (Rate Ratio [RR]=1.43 [95% CI = 1.05-1.93]); and 2) mean time between groin puncture and

reperfusion was slightly (~5 min), but not significantly greater in GA patients (RR=1.15 [95% CI = 0.77-1.70]).[18] In contrast, in the SWIFT PRIME trial, in which 36% of EVT patient received GA, neither the time between CT scan and groin puncture (median 52 minutes) nor the time between groin puncture and reperfusion (median 32 minutes) were significantly affected by GA (RR= 0.96 [95% CI = 0.81-1.13], and RR= 0.91 [95% CI = 0.74-1.13], respectively).[16] The authors of this review speculate that, in the ESCAPE trial, because GA was actively discouraged, the anesthesia team was not included in routine workflow and was requested to provide care only when problems (and associated delays) had already occurred. In contrast, in the SWIFT PRIME trial, because so many EVT patients received GA, there was a well-established system to include the anesthesia team early in EVT workflow, reducing delays associated with GA.

Table S3-1. Observational Reports Comparing Sedation and GA for EVT: EVT Workflow

Pre-EVT: Any interval starting at symptom onset and ending at start of EVT	Observational Report, Reference	Sedation	General Anesthesia	Difference in Group Means or Medians (Sedation-GA	P Value
Symptom onset to groin puncture (min)	Jangani et al., 2016 [1]	256±119	282±126	-26	0.22
	Whalin et al., 2014 [2]	292 (208-359)	304 (255-420)	-12	0.307
	Sugg et al., 2010 [3]	260 (212-372)	271 (237-335)	-11	0.802
	Abou-Chebl et al., 2010 [4]	296±172	306±133	-10	0.09
	Abou-Chebl et al., 2015 [5]	206 (80-341)	210 (110-315)	-4	NR
	Abou-Chebl et al., 2014 [6]	395±254	337±208	+58	0.04
Symptom onset to arterial access (min)	Li et al., 2014 [7]	276±120	300±138	-24	0.244
Symptom onset to start EVT (min)	Slezak et al., 2017 [8]	277±126	299±157	-22	0.165
Symptom onset to start of intra-arterial treatment, not otherwise specified (min)	van den Berg et al., 2015 [9]	220	241	-21	0.02
	Nichols et al., 2010 [10]	233	238	-5	NR
	Davis et al., 2012 [11]	275	275	0	0.173
	Bracard et al., 2017 [12]	252 (217-292)	243 (205-284)	+9	0.192
	Jumma et al., 2010 [13]	654±804	418±291	+236	0.04

In hospital workflow: Any interval with event starting in hospital and ending no later than reperfusion	Observational Report, Reference	Sedation	General Anesthesia	Difference in Group Means or Medians (Sedation-GA	P Value
Arrive emergency room to groin puncture (min)	Berkhemer et al., 2016 [14]	134±60	162±69	-28	NR, but significant
	Sugg et al., 2010 [3]	143 (105–174)	167 (120–195)	-24	0.504
	Abou-Chebl et al., 2014 [6]	141±91	142±91	-1	0.96
	Goyal et al., 2014 [15]	145	146	-1	NR
	Goyal et al., 2016 [16]	96	89	+7	0.76
Arrive emergency room to microcatheter (min)	Hassan et al., 2012 [17]	287±348	310±355	-23	0.78
Initial (CT) image to groin puncture (min)	Menon et al., 2016 [18]	51 (39-68)	73	-22	NR, but significant
Initial (CT) image to start procedure (min)	Just et al., 2016 [19]	270	229	+41	0.292
Initial (CT) image to first DSA (min)	Janssen et al., 2016 [20]	60 (44-72)	77 (68-91)	-17	0.001

Door to recanalization (min)	Langer et al., 2013 [21]	127±39	168±35	-41	0.02
Randomization to reperfusion (min)	Campbell et al., 2018 [22]	85 (51–118)	105 (80–149)	-20	<0.0001

Intra-EVT: Any interval with event starting between arrival to angiography suite and ending with leaving angiography suite	**Observational Report, Reference**	**Sedation**	**General Anesthesia**	**Difference in Group Means or Medians (Sedation-GA)**	**P Value**
Procedure duration, not otherwise specified (min)	Langer et al., 2013 [21]	99±38	134±63	-35	<0.01
	Nichols et al., 2010 [10]	113	142	-29	NR
	Just et al., 2016 [19]	212	239	-27	0.176
	Jangani et al., 2016 [1]	82±40	87±30	-5	0.23
	Berkhemer et al., 2016 [14]	79±41	76±35	+3	NR, NS
	Bracard et al., 2017 [12]	56 (24-86)	45 (28-70)	+11	0.547
Arrive angio suite to last angiogram (min)	Sugg et al., 2010 [3]	111 (80–147)	97 (75–109)	+14	0.583
Total procedure time, not otherwise specified (min)	Abou-Chebl et al., 2014 [6]	106±77	101±62	+5	0.6
Duration of intervention, not otherwise specified (min)	Mundiyanapurath et al., 2015 [23]	100 (75-160)	105 (72-195)	-5	0.80
Anesthesiologist starts case to groin incision (min)	John et al., 2014 [24]	19±11	23±13	-4	0.02
Groin incision to first angiographic run (min)	John et al., 2014 [24]	13±14	10±7	+3	0.087
Groin incision to reaching target vessel for thrombectomy (min)	John et al., 2014 [24]	35±19	29±15	+6	0.02
Groin puncture to first revascularization (min)	Menon et al., 2016 [18]	30 (18-46)	35	-5	NR, NS
Groin incision to recanalization (min)	John et al., 2014 [24]	78±41	85±52	-7	0.434
	Whalin et al., 2014 [2]	85±50	76±40	+9	0.172
Groin puncture to reperfusion (min)	Goyal et al., 2014 [15]	120	125	-5	NR
Groin puncture to last DSA run (min)	Menon et al, 2014 [25]	NR	NR	-13	0.029
Arterial access to arterial closure (min)	Li et al., 2014 [7]	84±42	126±66	-42	<0.001
First DSA to last vascular image	Janssen et al., 2016 [20]	35 (25-69)	41 (23-66)	-6	0.9

(min)					
Fluoroscopy time (min)	Abou-Chebl et al., 2014 [6]	40±33	28±22	+12	0.008
Time to revascularization, not otherwise specified (min)	Abou-Chebl et al., 2014 [6]	82±88	74±82	+8	0.3

Omnibus: Symptom onset to Reperfusion	**Observational Report, Reference**	**Sedation**	**General Anesthesia**	**Difference in Group Means or Medians (Sedation-GA**	**P Value**
Symptom onset to final DSA (min)	Menon et al, 2014 [25]	NR	NR	-40	NR
Symptom onset to recanalization (min)	John et al., 2014 [24]	436±189	510±538	-74	0.261
	Abou-Chebl et al., 2015 [5]	333 (285-374)	332 (280-376)	+1	NR
	Mundiyanapurath et al., 2015 [23]	276 (165-314)	270 (180-410)	+6	0.88
	Berkhemer et al., 2016 [14]	349±81	334±86	+15	NR, NS
Symptom onset to reperfusion (min)	Campbell et al., 2018 [22]	288 (222–358)	302 (246–357)	-14	0.57

Values are reported as mean ± SD or median (25^{th}-75^{th} percentiles). Underlined values indicate the values were calculated by the authors of this review based on information provided in the original publication. All P values were reported in the original publications.
Abbreviations: CT, computed tomography; DSA, digital subtraction angiogram; EVT, endovascular thrombectomy; GA, general anesthesia; NR, not reported in original publication; NS, not significant.

Hypothesis #2: Outcome Differences between Sedation and GA are Due to Blood Pressure Differences

EVT patients have a high incidence of chronic hypertension and, in addition, there is an acute hypertensive response to stroke.[26] Most EVT patients will be at least moderately hypertensive at presentation. Systolic blood pressures (BPs) are typically 140-150 mm Hg,[27-29] but systolic BPs in the 160-180's are common.[30,31] Likewise, at presentation, mean arterial pressure (MAP) is typically 100-110 mm Hg.[30-34] Two different EVT studies, one conducted with GA[32]] and one conducted with sedation,[33] both showed decreases in MAP prior to reperfusion were associated with less favorable neurologic outcome.

The observational report by Davis *et al.* was the first to describe intra-EVT hemodynamics.[11] EVT patients selected to receive sedation had: 1) greater values for minimum intra-EVT systolic BP (SBP_{MIN}) than patients who were selected to receive GA (134±32 vs. 104±15 mmHg, respectively; P<0.001); and 2) greater values for minimum intra-EVT mean arterial pressure (MAP_{MIN}) (97±13 vs. 71±10, respectively, P<0.001).[11] Combining the sedation and GA groups, SBP_{MIN} <140 mmHg was associated with poor outcome: RR=0.59; 95% CI=0.49-0.87; P=0.008. An intra-EVT SBP_{MIN} <140 mmHg was present in 40% of the sedation patients vs. 96% of the GA patients; P<0.0001. This was the first report to provide evidence that sedation vs. GA outcome differences might be the basis of greater incidence and/or severity of relative hypotension in patients selected to receive GA. This hypothesis is mechanistically compatible with: 1) the importance of collateral perfusion to maintain penumbral viability prior to reperfusion and; 2) collateral perfusion being at least partially BP dependent.

Table S3-2 summarizes observational studies regarding intra-EVT BP and outcome. Inspection of Table S3-2 suggests the following general relationships may be present. First, when MAP_{MIN} in the sedation and/or GA group is less than 70-80 mm Hg, there is an association between MAP_{MIN} and neurologic outcome.[1,2,11,32,33,35] Second, sedation vs. GA outcome differences appear to be related to the magnitude of the sedation vs. GA MAP_{MIN} difference until MAP_{MIN} in the GA group exceeds 80 mm Hg.[1,2, 11] Third, in reports in which MAP_{MIN} in the sedation and GA groups exceed 80 mm Hg, there is not a detectable relationship between MAP_{MIN} and outcome, nor is there outcome difference between sedation and GA.[8,36-38]

Thus, observational reports suggest outcome may be related to MAP_{MIN}, with a lower threshold of at least 70-80 mm Hg,[2,35] although, in some studies, a lower threshold of 100 mmHg appears to be present.[11,32,33] Whalin et al. reported MAP_{MIN} thresholds appear to vary among patients depending on the severity of their initial stroke symptoms.[33] Because, in any given EVT patient, it is not possible to know their individual tolerance for decreased BP, a reasonable management principle is to try to avoid any substantive decrease in BP prior to reperfusion, regardless of method of anesthesia.

Table S3-2. Observational Reports Comparing Sedation and GA for EVT: BP and Outcome

Observational Report, Reference	Pre-EVT MAP	MAP_{MIN}, Sedation	MAP_{MIN}, General Anesthesia	Mean MAP_{MIN} Difference (Sedation-GA)	Relationship Between Intra-EVT BP and Neurologic Outcome[a]	Sedation Versus GA and Neurologic Outcome (mRS)[a]
Löwhagen Hendén et al. 2015 [35]	107 (93-120)	NA	60 (55-66)	NA	↓ MAP_{MIN} >40% associated with poor mRS: OR=0.36 (95% CI=0.14-0.92); P=0.032. Based on pre-EVT MAP=107 mm Hg, estimated MAP_{MIN} threshold=64 mm Hg.	NA
Treurniet et al., 2017 [32]	100 (92-110)	NA	60 (55-69)	NA	↓MAP_{MEAN} associated with poor mRS: per 10 mm Hg ↓ below pre-EVT MAP (100 mmHg) OR=0.60 (95% CI=0.43-0.90); P=0.03	NA
Whalin et al., 2017 [33]	107 (95-120)	79 (71-89)	NA	NA	↓ MAP_{MIN} associated with poor mRS: per 10 mmHg below 100 mm Hg OR=0.78 (95% CI=0.62-0.99); P=0.043.	NA
Jagani et al., 2016 [1]	NR	79±14	62±11	17 (P=0.007)	MAP_{MIN} associated with mRS: 71±15 mmHg (poor mRS) vs. 78±16 mm Hg (good mRS); P=0.06	GA associated with poor mRS; P=0.02.
Whalin et al., 2014 [2]	107±19	74±9	69±9	5 (P=0.001)	MAP_{MIN} <70 mm Hg associated with poor mRS: per 10 mm Hg below OR=0.34 (95% CI=0.16-0.72); P=0.005	GA not associated with poor mRS: OR=0.68 (95% CI=0.32-1.43); P=0.306.
Davis et al., 2012 [11]	NR	97±13	71±10	26 (P<0.001)	SBP_{MIN} <140 mm Hg associated with poor mRS: RR=0.59 (95% CI=0.49-0.87); P=0.008. Based on reported MAP/SBP ratio=0.7, estimated MAP_{MIN} threshold=98 mm Hg.	GA associated with poor mRS: RR=0.31 (95% CI=0.14-0.66); P=0.002.
John et al., 2014 [24]	107±22	89±15	72±15	17 (P=0.33)	Not formally assessed	GA not associated with poor mRS: OR=0.64 (95% CI=0.25-1.64); P=0.35
Takahashi et al., 2014 [36]	109 (NR)	NA	83 [est]	NA	mRS not associated with any BP metric	NA
Sivasankar et al., 2016 [37]	106±18	87 [est]	85 [est]	2 [est] (NR)	mRS not associated with any BP metric	Anesthesia type associated with mRS (P=0.048) with best apparent outcome with volatile-only based GA.

Mundiyanapurath, et al. 2016 [38]	121 [est]	NA	87 [est]	NA	mRS not associated with any BP metric	NA
Slezak et al., 2017 [8]	NR	115 [est]	102 [est]	13 [est] (NR)	Difference between sedation and GA in ↓ intra-EVT BP not associated with outcome[b]	GA not associated with poor mRS: OR=0.87 (95% CI=0.51-1.51); P=0.620.

Values are reported as mean ± SD or median (25^{th}-75^{th} percentiles). Data are ordered on the basis of increasing MAP_{MIN} in the GA group. Underlined values indicate the values were calculated by the authors of this review based on information provided in the original publication. P values were reported in the original publications.

Abbreviations: BP, blood pressure; CI, confidence interval; [est], estimate; EVT, endovascular thrombectomy; GA, general anesthesia; MAP, mean arterial pressure; $MAP_{MEAN,}$ mean of mean arterial pressure during EVT; MAP_{MIN}, minimum mean arterial pressure during EVT; mRS, modified Rankin Scale; NA, not applicable; NR, not reported in original publication; OR, odds ratio; RR, rate ratio; SBP, systolic blood pressure.

[a] Poor mRS is defined as any mRS score ≥3.

[b] Slezak et al. did not report or compare intra-EVT MAP. However, there was a significantly greater decrease in intra-EVT SBP in patients selected to receive GA.

Hypothesis #3: EVT Patients Selected to Receive Sedation Require Vasopressors Less Often and/or At Lesser Doses than Patients Selected to Receive GA

Based on the immediately preceding discussion, is reasonable to hypothesize anesthetic management that either: 1) maintains BP; and/or 2) quickly reverses decreases in BP during EVT might result in better outcomes. However, it is not known with certainty that is true. It is also possible EVT patients who have the greatest decreases in BP in response to sedatives, analgesics, and anesthetics have co-morbidities that independently contribute to less favorable outcome (e.g., atrial fibrillation[39,40]).

As summarized in Table S3-3, most, but not all, observational reports suggest patients who were selected to receive sedation had greater intra-EVT BP than patients who were selected to receive GA.[1,2,8,11,23] In one report, the BP difference sedation and GA was independent of patient co-morbidity.[1] Lower BP in patients selected to receive GA was observed despite the fact that GA patients more often received vasopressors than patients selected to receive sedation[1,2, 8, 27] and/or received a greater vasopressor dose.[23]

Observational reports indicate nearly all GA patients received a pressor during EVT, regardless of the anesthetic agents used.[1,2,8,24,32, 35,37,38] However, as shown in Table S3-3, substantive decreases in BP often occurred in patients who were selected for sedation. In the observational report by John et al., 22/37 (60%) of EVT patients selected to receive propofol-based sedation received phenylephrine (0.08 mcg/kg/min [estimate]) to achieve a group mean MAP_{MIN} = 77±10 mmHg.[41] In this same report, 27/35 (77%) of EVT patients selected to receive dexmedetomidine-based sedation received phenylephrine (0.28 mcg/kg/min [estimate]) to achieve a group mean MAP_{MIN} = 67±17. In a continuation of their 2014 report,[2] in 2017 Whalin *et al*. reported 134/256 (52%) of EVT patients who received dexmedetomidine-based sedation received phenylephrine (dose not reported), to achieve a group mean MAP_{MIN} = 79 (25-75% percentile:71-89).[33] Mundiyanapurath *et al.* reported EVT patients receiving sedation consisting of propofol (5 mcg/kg/min [estimate]) and remifentanil (0.024 mcg/kg/min [estimate]) required a mean norepinephrine dose of 0.025 mg/kg/min [estimate] to maintain BP close to pre-EVT values.[23] Finally, Slezak et al. reported 54/134 (40%) of EVT patients selected to receive intermittent boluses of midazolam (2.5 mg), fentanyl (50 mcg), and /or propofol (20 mg) required a vasopressor during EVT (dose not reported).[8] Thus, observational reports suggest, regardless of the specific agents used, at least half of EVT patients selected to receive sedation require vasopressors to maintain BP close to pre-EVT values.

Table S3-3. Observational Reports Comparing Sedation and GA for EVT: Medications, Doses, Hemodynamics and Vasopressors

Observational Report, Reference	Anesthetic Agents and Doses		Intra-EVT Hemodynamics	Intra-EVT Vasopressor Administration (incidence)			Vasopressor Type and Dose
	Sedation	General Anesthesia		Sedation	General Anesthesia	P Value	
Davis et al., 2012 [11]	n=48. Fentanyl (25 mcg). Midazolam (2.5 mg). "Every 15 to 30 minutes."	n=48. NR	Systolic BP_{MIN} and MAP_{MIN} greater in Sedation Group	NR	NR	NA	NR
John et al., 2014 [24]	n=99. One or more: Propofol infusion, Dexmedetomidine infusion, Fentanyl, Midazolam "as needed." Doses NR.	n=91. NR except use of neuromuscular blockers	Systolic BP_{MIN} and MAP_{MIN} did not differ between Sedation and GA	59/99 (60%)	59/91 (65%)	0.457	NR
Whalin et al., 2014 [2]	n=83. Dexmedetomidine: load (optional) 0.5 mcg/kg; infusion 0.3-1.0 mcg/kg/h. Midazolam or Fentanyl "as needed. " Doses NR.	n=133. NR	MAP_{MEAN} and MAP_{MIN} greater in Sedation Group	45/78 (58%)	104/133 (79%)	0.001	NR
Mundiyanapurath et al., 2015 [23]	n=15. Propofol: 5 mcg/kg/min [est] and Remifentanil: 0.024 mcg/kg/min [est]	n=29. Propofol: 48 mcg/kg/min [est] and Remifentanil: 0.12 mcg/kg/min [est]	Systolic BP_{MEAN} greater in Sedation Group	NR	NR	NA	Norepinephrine. Sedation: 0.025 mcg/kg/min[est]. GA: 0.10 mcg/kg/min [est]; P=0.001
Sivasankar et al., 2016 [37]	n=7. Fentanyl: 4/7 (57%). Remifentanil: 1/7 (14%). Dexmedetomidine: 1/7 (14%). Propofol: 1/7 (14%). Doses NR	n=77. **Volatile only** 35/77 (45%): Desflurane (80%) or Sevoflurane (20%) <0.5 MAC. **TIVA** 12/77 (16%): Propofol infusion (40-140 mcg/kg/min) and Fentanyl bolus (dose NR). **Combined** 30/77 (39%): volatile <0.5 MAC and propofol infusion 30-140 mcg/kg/min.	MAP_{MEAN} (~90±10 mmHg) did not differ among 4 anesthesia groups	1/7 (14%)	**Volatile only**: 31/35 (89%). **TIVA**: 11/12 (92%). **Combined**: 27/30 (90%). All 3 GA groups: 69/77 (90%)	NR, <0.0001	Phenylephrine, Epinephrine, Ephedrine. Doses NR
Jagani et al., 2016 [1]	n=61. Fentanyl: 39/42 (93%). Midazolam: 24/42 (24%). Propofol: bolus 3/42 (7%) or infusion 7/42 (17%). Doses NR	n=38. Volatile (Isoflurane, Sevoflurane, Desflurane): 37/38 (97%). Nitrous oxide: 4/38 (11%). Propofol infusion: 4/38 (11%). Doses NR	Systolic BP_{MIN} and MAP_{MIN} greater in Sedation Group	34/55 (58%)	33/37 (89%)	0.004	Phenylephrine, Epinephrine, Ephedrine. Doses NR.
Slezak et al., 2017 [8]	n=135. Intermittent bolus: Midazolam (2.5mg). Fentanyl (50 mcg). Propofol (20 mg).	n=266. Propofol infusion 100-167 mcg/kg/min. Fentanyl 1-3 mcg/kg	Systolic BP_{MIN} greater in Sedation Group	54/134 (40%)	254/265 (96%)	<0.001	NR
John et al., 2015 [41]	n=72**. Dexmedetomidine infusion**: 35/72 (49%); dose NR. **Propofol infusion**: 37/72 (51%); dose NR. Fentanyl bolus 43/72 (60%); ~75±50 mcg. Midazolam bolus: 16/72 (22%); ~1.5±1.0 mg	NA	Systolic BP_{MIN} and MAP_{MIN} greater in Propofol group	**Dexmedetomidine**: 27/35 (77%) **Propofol:** 22/37 (60%). P=0.106	NA	NA	Phenylephrine. **Dexmedetomidine**: 0.28 mcg/kg/min [est] **Propofol**: 0.08 mcg/kg/min [est]. P=0.007

Values are reported as incidence (percentage) or mean. Underlined values indicate the values were calculated by the authors of this review using data provided in the original publication. P values were reported in the original publications, except when indicated by an underline (calculated by the authors of this review using Fisher's exact test).
Abbreviations: BP_{MEAN}, mean of blood pressure; BP_{MIN}, minimum blood pressure; [est], estimate based on mean body weight of 70 kg; EVT, endovascular thrombectomy; GA, general anesthesia; MAC, minimum anesthetic concentration; $MAP_{MEAN,}$ mean of mean arterial pressure during EVT; MAP_{MIN}, minimum mean arterial pressure during EVT; NA, not applicable; NR, not reported in original publication; TIVA, total intravenous anesthesia.

Hypothesis #4: The majority (>50%) of EVT Patients Selected to Receive Sedation but Who were Converted to GA were Because of "Agitation."

Of the 24 observational reports comparing sedation and GA for EVT, 13 reported the percentage of patients selected for sedation who required conversion to GA; see Table S3-4. The incidence of sedation-to-GA conversion ranged between 0% and 14%, with an overall average of 51/1,184 (4.3%). Thus, when *selected* to receive sedation for EVT, only a small minority of patients (≤ 5%) required conversion to GA during EVT. Of these 13 reports, 9 reported the agents used for sedation. Inspection of Table S3-4, does not suggest an obvious relationship between the selected sedatives and the need to convert to GA. In these 13 reports, 10 reported the reasons for sedation failure, with some patients having more than one reason. By far, the most commonly reported reason for sedation-to-GA conversion was "agitation," followed by respiratory failure, obtundation, and emesis.

The authors of this review speculate: 1) the low apparent incidence of sedation failure in observational reports may be due to selection bias and, in *non-selective* circumstances (e.g., in RCTs), the sedation failure rate may exceed 5%; and 2) patients who show signs of "agitation" and/or other signs of not being able to remain motionless *before starting* EVT may be most those most likely to fail sedation.

Table S3-4. Observational Reports Comparing Sedation and GA for EVT: Sedation-to-GA Conversion During EVT

Observational Report, Reference	Sedation Agents and Doses	Sedation-to-GA Conversion	Agitation	CNS Problem	Emesis	Respiratory Problem
Sivasankar et al., 2016 [37]	Fentanyl: 4/7 (57%). Remifentanil: 1/7 (14%). Dexmedetomidine: 1/7 (14%). Propofol: 1/7 (14%). Doses NR	0/7 (0%)	0	0	0	0
Janssen et al., 2016 [20]	Remifentanil. Dose NR	0/31 (0%)	0	0	0	0
John et al., 2014 [24]	One or more: Propofol infusion, Dexmedetomidine infusion, Fentanyl, Midazolam "as needed." Doses NR	1/99 (1.0%)	0	1	0	NR
Just et al., 2016 [19]	NR	1/68 (1.5%)	1	0	0	0
Jagani et al., 2016 [1]	Fentanyl: 39/42 (93%). Midazolam: 24/42 (24%). Propofol: bolus 3/42 (7%) or infusion 7/42 (17%). Doses NR	1/62 (1.6%)	NR	NR	NR	NR
Jumaa et al., 2010 [13]	One or more: Ketamine, Propofol, Fentanyl, Midazolam, Dexmedetomidine. Doses NR	2/73 (2.7%)	1	1	1	0
Langer et al., 2013 [21]	Midazolam or Diazepam (2-3 mg), Piritramide (1 mg)	3/108 (2.8%)	0	1	0	2
Hassan et al., 2012 [17]	NR	3/86 (3.4%)	2	0	1	1
van den Berg et al., 2015 [9]	NR	10/278 (3.6%)	9	0	0	1
Berkhemer et al., 2016 [14]	NR	6/137 (4.4%)	6	0	0	0
Slezak et al., 2017 [8]	Intermittent bolus: Midazolam (2.5 mg). Fentanyl (50 mcg). Propofol (20 mg).	10/135 (7.4%)	NR	NR	NR	NR
Mundiyanapurath et al., 2015 [23]	Propofol: 5 mcg/kg/min [est] and Remifentanil: 0.024 mcg/kg/min [est]	2/17 (11.8%)	2	0	0	0
Whalin et al., 2014 [2]	Dexmedetomidine: load (optional) 0.5 mcg/kg; infusion 0.3-1.0 mcg/kg/h. Midazolam or Fentanyl "as needed." Doses NR	12/83 (14.4%)	NR	NR	NR	NR
Total		**51/1,184 (4.3%)**	**21**	**3**	**2**	**4**

Values are reported as incidence (percentage). Data are presented in ascending order of sedation-to-GA conversion incidence. Underlined values indicate the values were calculated by the authors of this review using data provided in the original publication.

Abbreviations: CNS, central nervous system; [est], estimate based on body weight of 70 kg; EVT, endovascular thrombectomy; GA, general anesthesia; NR, not reported in original publication.

Hypothesis #5: GA May Slightly Increase the Incidence of Adequate Reperfusion, but the Difference is Probably Too Small to Detect Statistically without a Very Large RCT

EVT effectiveness depends on the restoration of an adequate level of reperfusion (mTICI class 2b-3). Not all observational reports provide the percentage of EVT patients who had adequate reperfusion; Table S3-5 summarizes the findings of the 16 observational reports that did.

Table S3-5. Observational Reports Comparing Sedation and GA for EVT: Adequate Reperfusion

Observational report, Reference	Adequate Reperfusion,[a] Sedation	Adequate Reperfusion,[a] General Anesthesia	P Value
Nichols et al., 2010 [10]	24/33 (73%)	7/20 (35%)	0.01
Sugg et al., 2010 [3]	43/57 (75%)	6/9 (67%)	0.331
Jumaa et al., 2010 [13]	60/73 (82%)	37/ 53 (70%)	0.103
Langer et al., 2013 [21]	62/105 (59%)	11/19 (58%)	NR
Li et al., 2014 [7]	56/74 (76%)	22/35 (63%)	0.392
John et al., 2014 [24]	47/97 (49%)	52/90 (58%)	0.182
Whalin et al., 2014 [2]	70/83 (84%)	96/133 (72%)	0.039
Abou-Chebl et al., 2014 [6]	72.9%[b]	73.6%[b]	0.9
Abou-Chebl et al., 2015 [5]	131/180 (73%)	94/123 (76%)	0.48
van den Berg et al., 2015 [9]	113/265 (43%)	34/70 (49%)	0.37
Mundiyanapurath et al., 2015 [23]	8/15 (53%)	20/29 (68%)	0.28
Janssen et al., 2016 [20]	25/31 (80%)	43/53 (81%)	NR
Berkhemer et al., 2016 [14]	86/137 (63%)	41/79 (52%)	0.19
Bracard et al., 2016 [12]	43/69 (62%)	51/67 (76%)	0.059
Slezak et al., 2017 [8]	116/135 (86%)	235/266 (88%)	0.488
Campbell et al., 2018 [22]	386/507 (76%)	160/213 (75%)	0.78

Values are incidence (percent). Underlined values indicate the value was calculated by the authors of this review based on information provided in the original publications. P values were reported in the original publications.

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

a. Adequate perfusion is defined as Modified Thrombolysis in Cerebral Infarction (mTICI) classes 2b, 2c or 3 (denoted 2b-3).

b. Only percentages reported in original publication, and it is not possible to estimate numerators and denominators.

The first observational reports comparing sedation and GA reported numerically greater reperfusion rates in patients selected for sedation. [3,7,10,13] These observations may reflect selection bias, because there was a greater incidence of intracranial carotid occlusions[7,10] and/or posterior circulation occlusions[7] in patients selected for GA. However, with subsequent reports, the incidence of adequate reperfusion appears to have equalized between patients selected for sedation and GA. Although not achieving statistical significance, several reports observed numerically greater rates of adequate reperfusion in patients selected for GA, despite the potential for selection bias against GA.[5,8,9,12,23,24] In the first observational report of sedation vs. GA to exclusively use retrievable stents, the incidence of adequate reperfusion (mTICI 2b-3) did

not differ between sedation and GA (72.9% vs. 73.6% respectively; P=0.9).[6] However, in that report, the percentage of patients who received ≥ 3 device passes was less in those selected for sedation that in those selected for GA, 11/84 (13%) vs. 55/196 (28%), respectively; Fisher's exact P=0.0086 calculated by the authors of this review. This observation suggests patients selected to receive GA had, either: 1) more complex occlusions; and/or 2) interventionists may have had greater willingness to continue attempts to achieve adequate reperfusion better operating conditions. The authors of this review speculate that, when EVT is conducted with sedation and operating conditions are poor and/or patient neurologic or cardio-respiratory status are tenuous, interventionists may sometimes accept "good enough" reperfusion rather than making additional attempts to achieve best possible reperfusion. In contrast, with GA, good working conditions may support additional attempts at complete reperfusion.

Nevertheless, if there were better reperfusion with GA, it is not likely that it could be detected statistically because of the small absolute difference between sedation and GA. Based on the current incidence of adequate reperfusion achieved with sedation of 80%, using chi-square test and planned 80% statistical power with a Type I error rate of 0.05, to detect an absolute increase of 5%—to 85% adequate reperfusion with GA—would require ~900 patients in both groups. Therefore, even if GA might facilitate EVT and increase the incidence of adequate reperfusion, only a very large RCT would have sufficient power to detect it.

Hypothesis #6: GA May Slightly Decrease the Incidence of Endovascular Complications, but the Difference is Probably Too Small to Detect Statistically without a Very Large RCT

A potential limitation of performing EVT under sedation is that patient motion may result in roadmap/fluoroscopy misalignment and/or unwanted motion at critical moments such that endovascular complications (intracranial vessel dissection and/or perforation) may occur. Not all observational reports have reported the percentage of patients with intra-EVT dissection/perfusion; Table S3-6 summarizes the findings of the 11 that did. There is substantial heterogeneity among the reports in the incidence of endovascular complications (0% to 26%), but the incidence appears to have decreased over the years of use of EVT to now be ≤3-5%. The observational data does not suggest endovascular complications are less common with GA, although the largest and most recent observational report is consistent with that possibility.[22]

If present, is not likely that a lower incidence of endovascular complications with GA could be statistically verified because of the small absolute difference between sedation and GA. Based on the current incidence of endovascular complications with sedation of 3%, having an 80% statistical power to detect even a 50% reduction in the incidence with GA (to 1.5%) with alpha=0.05 would require using chi-square test ~1,530 patients in both groups. Therefore, even if GA might contribute to a lesser incidence of endovascular complications, only a very large RCT would have sufficient power to detect it.

Table S3-6. Observational Reports Comparing Sedation and GA for EVT: Endovascular Complications

Observational Report, Reference	Intracranial Dissection or Perforation, Sedation	Intracranial Dissection or Perforation, General Anesthesia	P Value
Nichols et al., 2010 [10]	0/49 (0%)	1/26 (4%)	0.35
Sugg et al., 2010 [3]	2/57 (4%)	2/9 (22%)	NR
Jumaa et al., 2010 [13]	5/73 (7%)	8/53 (15%)	0.13

Langer et al., 2013 [21]	0/105 (0%)	1/19 (15%)	NR
Li et al., 2014 [7]	19/74 (26%)	9/35 (26%)	0.997
van den Berg et al., 2015 [9]	16/278 (6%)	2/70 (3%)	NR
Janssen et al., 2016 [20]	0/31 (0%)	0/53 (0%)	NR
Berkhemer et al., 2016 [14]	4/137 (3%)	2/79 (3%)	NR
Jagani et al. , 2016 [1]	0/61 (0%)	1/38 (3%)	NR
Slezak et al., 2017 [8]	8/135 (6%)	17/266 (6%)	NR
Campbell et al., 2018 [22]	9/561 (1.6%)	1/236 (0.4%)	0.3

Values are incidence (percent). P values were reported in the original publications.
Abbreviations: EVT, endovascular thrombectomy; GA, general anesthesia; NR, not reported in original publication.

Hypothesis #7: Because Stroke-Associated Pneumonia is Related to National Institutes of Health Stroke Scale (NIHSS) Score, the Greater Incidence of Post-EVT Pneumonia in Patients Selected for GA May Be Due to Selection Bias

Not all observational reports comparing sedation and GA reported the percentage of patients who had post-EVT pneumonia; Table S3-7 summarizes the unadjusted data of the 12 reports that did. The heterogeneity among reports in reported pneumonia incidence was likely due to differing diagnostic criteria. Five observational reports found a statistically significant greater incidence of postoperative pneumonia in patients selected to receive GA.[2,8,10,13,42] In 6 of the remaining 7 reports, pneumonia was observed more commonly in patients selected to receive GA, but was not statistically significant.[7,14,17, 21,22,43] NIHSS score is a strong predictor of pneumonia in stroke patients.[44] In 4 of 5 reports in which pneumonia was significantly greater in patients selected for GA, NIHSS score was also significantly greater in the GA group.[2,8,10,13] Of the 3 reports in which NIHSS score was not significantly greater in GA patients,[9,14,22] observed pneumonia incidences were only 3-5% (absolute) greater in patients selected for GA in 2 reports[14,22] and was 2% less in patients selected for GA in 1 report.[9] Thus, the greater incidence of post-EVT pneumonia observed in patients selected to receive GA may be due, at least in part, to selection bias.

Table S3-7. Observational Reports Comparing Sedation and GA for EVT: Post-EVT Pneumonia

Observational Report, Reference	Pneumonia, Sedation	Pneumonia, General Anesthesia	P Value
Nichols et al., 2010 [10]	4/49 (8%)	8/26 (31%)	0.02
Jumaa et al., 2010 [13]	10/73 (14%)	16/53 (30%)	0.024
Hassan AE, 2012 [17]	12/83 (14%)	12/53 (23%)	NR, 0.25
Langer et al., 2013 [21]	15/105 (14%)	4/19 (21%)	NR, 0.49
Li et al., 2014 [7]	12/74 (16%)	7/35 (20%)	0.584
Whalin et al., 2014 [2]	7/82 (8%)	40/128 (31%)	<0.001
McDonald et al., 2015 [42]	47/507 (9%)	86/507 (17%)	0.0005
van den Berg et al., 2015 [9]	41/278 (15%)	9/70 (13%)	0.69
Berkhemer et al., 2016 [14]	13/137 (9%)	11/79 (14%)	NR, 0.37
Bekelis et al., 2017 [43]	NR	NR	NR, NS[a]
Slezak et al., 2017 [8]	22/135 (16%)	67/265 (25%)	0.048
Campbell et al., 2018 [22]	47/561 (8%)	27 /235 (11%)	0.18

Values are incidence (percent). Underlined values indicate the value was calculated by the authors using data provided in the original publication. P values were reported in the original publications, except when indicated by an underline, which were calculated by the authors of this review using Fisher's exact test. Abbreviations: EVT, endovascular thrombectomy; GA, general anesthesia; NR, not reported in original publication; NS, not significant.

[a] Bekelis et al., 2017, reported the incidence of post-EVT pneumonia was 2.3% (absolute) greater in patients who were selected for GA, but this was not statistically significantly greater than pneumonia incidence in patients who were selected for sedation.

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