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Is peri-procedural sedation during acute stroke therapy associated with poorer functional outcomes?

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Abstract

Background—To safely perform acute intra-arterial (IA) revascularization procedures, use of sedative medications and paralytics is often necessary. During the conduct of the Interventional Management of Stroke (IMS) trials (I and II), we noted that the level of sedation used peri-procedurally varies. At some institutions, patients are paralyzed and intubated as part of procedural standard of care, while at other institutions no routine sedation protocol is followed. We sought to identify patient characteristics that would correlate with the need for deeper sedation and to explore whether levels of sedation relate to patient outcomes.

Methods—We studied 75 of 81 patients in the IMS II Study who had anterior circulation strokes and underwent angiography and/or intervention. We defined four sedation categories, and tested for factors potentially associated with the level of sedation. We also analyzed clinical outcomes including successful angiographic reperfusion and the occurrence of clinical complications.

Results—Only baseline NIHSS varied significantly by sedation category ($p=0.01$). Patients that were in the lower sedation category fared better, having a higher rate of good outcomes ($p<0.01$), lower death rates ($p=0.02$), and higher successful angiographic reperfusion rates ($p=0.01$). We found a significantly higher infection rate in patients receiving heavy sedation or pharmacologic paralysis ($p=0.02$) and a trend toward fewer groin related complications.

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Conclusion—In this small sample, patients not receiving sedation fared better, had higher rates of successful angiographic reperfusion, and had fewer complications. Further examination of the indications for procedural sedation or paralysis and their effect on outcome is warranted.

Background

A myriad of clinical factors govern outcomes in stroke patients. While initial stroke severity, age, timeliness of thrombolytic therapy, and reperfusion are well-established predictors, others are poorly understood or not yet identified.[1,2,3] As intra-arterial (IA) procedures become used more frequently in clinical practice to treat acute ischemic stroke, defining procedure-related variables that affect patient outcomes is paramount.

During the conduct of the Interventional Management of Stroke (IMS) pilot trials (I and II), we noted that the level of sedation used peri-procedurally varies greatly.[4,5] At some institutions, patients are electively paralyzed and intubated as part of procedural standard of care, while at other institutions, no routine sedation protocol is followed.

To safely perform acute intra-arterial (IA) revascularization procedures, use of sedative medications and paralytics is often necessary. Unwanted patient movement during catheter manipulation could have disastrous consequences. On the other hand, stroke recovery may be adversely affected by sedatives, paralytics, and intubation both directly, due to direct CNS effects, or indirectly, by leading to medical complications such as ventilator-related pneumonia. Delays in start of intra-arterial procedure can also occur while waiting for anesthesia to provide deep sedation and intubation. Unfortunately, teasing out the effect of individual drugs, practices of medication administration, and decisions regarding intubation is difficult. Further, dosing, duration, and timing may be important with regard to the occurrence of adverse effects.[6,7]

We retrospectively analyzed the Interventional Management of Stroke II (IMS II) trial to: (1) document the variability in sedation patterns used for intra-arterial revascularization procedures, (2) identify clinical factors that were associated with the use of higher levels of sedation and (3) determine whether use of higher sedation was associated with poorer clinical outcome or the occurrence of complications.

Materials and Methods

The IMS II trial was a 13-center, open-label, single-arm pilot study of moderate-to-severe ischemic strokes (NIHSS≥10) treated with combined IV/IA rt-PA therapy within three hours of stroke symptom onset. The details of the trial design and results have been published previously.[4] In brief, the objectives of the trial were to: (1) obtain reliable estimates of the safety of combining low-dose IV rt-PA (0.6 mg/kg) followed by delivery of additional IA rt-PA(up to 22 mg) and low-energy ultrasound via the EKOS microcatheter; (2) consider the efficacy of combined IV/IA rt-PA treatment at three months as compared with the three-month outcomes of placebo-treated patients in the NINDS rt-PA Stroke trial; and (3) determine whether the recanalization rate of combined IV rt-PA followed by IA rt-PA and low-intensity ultrasound energy is greater than the rate of recanalization for the IMS I study subjects treated only with combined IV/IA rt-PA via a standard micro-catheter.[1,3]

Subjects were treated with low-dose IV rt-PA and concurrently taken to angiography for potential IA rt-PA therapy. If no thrombus was seen on angiography, no further treatment was provided. As part of the study protocol, clinicians performed formal NIH Stroke Scale Score (NIHSS) examinations just prior to IV treatment, again just before to initiation of IA therapy, and then at the completion of IA therapy. As part of the NIHSS examination, clinicians were asked to determine (1) whether patients were sedated, (2) whether sedation affected scoring on the NIHSS, and (3) whether the patient was intubated and/or paralyzed. For the purposes of this analysis, we defined four levels of sedation: (1) "no sedation" as being cases where no sedative medications were received, (2) "mild sedation" as being cases where sedative medications were administered, but those in which the sedation did not affect the patient's exam by clinical judgment, (3) "heavy sedation" as that which did affect the exam by clinical judgment, and (4) "pharmacological paralysis" as being cases where patients were intubated and/or paralyzed. We also considered sedation as a dichotomous variable consisting of "low sedation" if in the first two categories and "heavy sedation" if in the latter two categories. Sedation categories were determined based on the NIHSS evaluation immediately after the angiographic procedure. In five of 75 cases, no sedation score was available post-angiography, and the pre-angiography sedation score was used instead.

We limited the analysis to all IMS II cases with anterior circulation strokes that underwent angiography and/or intervention. Our primary interest was to determine baseline characteristics associated with sedation level. Due to small cell sizes, Fisher's exact tests were used to test for associations between categorical variables. Analysis of variance (ANOVA) models were used to test for association between categorical and continuous variables; to account for small cell sizes, or where the residuals appeared to violate the normality assumption of the ANOVA model, the non-parametric Kruskal-Wallis test was used instead.

As a secondary analysis, we used logistic regression to determine whether sedation (no/mild sedation versus heavy sedation/pharmacological paralysis) was associated with good outcome (modified Rankin Score 0–2), death, or successful angiographic reperfusion (TIMI grade 2–3). Baseline characteristics associated with outcome were considered for inclusion in the multivariable model, and a stepwise selection procedure was used to select covariates for inclusion in the final model.

We also analyzed complications that occurred with respect to sedation category. Rates of symptomatic and asymptomatic intracerebral hemorrhage, significant infections (including pneumonia, sepsis and other infections, but excluding urinary tract infections), access-site related complications (including groin hematomas, local bleeding, arterial occlusions, and retroperitoneal hematomas), cervical or intracranial vessel dissection or perforation, and acute myocardial infarction were compared.

Results

Of the 81 patients in the IMS II study, 78 met the inclusion criteria for this analysis. Three of these 78 cases were excluded because sedation data were not available before or after angiography. Among the 75 remaining cases, 40 (53%) received no sedation and 17 (23%) were pharmacologically paralyzed. Baseline characteristics across the four sedation categories are presented in Table 1. Only baseline NIHSSS varied significantly between the different levels of sedation ($p=0.03$). Using dichotomized sedation categories, there was a trend toward higher sedation categories being associated with aphasia, ICA occlusion, and longer procedure duration ($p \leq 0.06$). Due to the small numbers of patients per center, no analysis of center-specific sedation patterns was performed.

Table 2 lists outcomes as defined by sedation category. Patients that were in the lower sedation category fared better, having a higher rate of good outcomes, a lower death rate, and more frequent successful reperfusion.

Good outcome (mRS 0–2)

Sedation (p<0.01), gender (p<0.01), and baseline NIHSS (p<0.01) were associated with outcome in univariate analyses. Only mild or no sedation (OR 5.7; 95% CI 1.8, 17.8; p<0.01) and male gender (OR 4.2; 95% CI 1.5, 12.3; p<0.01) were independently associated with good clinical outcome.

Death

Sedation (p=0.02), baseline NIHSS (p=0.03), baseline systolic blood pressure (p=0.05) and baseline glucose (p=0.05) were associated with death in univariate analyses. The sedation category of heavy sedation or pharmacological paralysis (OR 5.0; 95% CI 1.3, 18.7; p=0.02) was the only independent predictor of death.

Angiographic Reperfusion

Of the 75 patients included in our analysis, 22 additional patients were excluded from the analysis of reperfusion because they did not undergo revascularization therapy and therefore had no TIMI grades. Sedation (p=0.01), baseline NIHSS (p=0.03), and ICA occlusion (p=0.04) were associated with reperfusion in univariate analyses. Mild or no sedation (OR 3.9; 95% CI 1.1, 13.9; p=0.04) and no ICA occlusion (OR 6.1; 95% CI 1.3, 27.9; p=0.02) were the only independent predictors of successful reperfusion.

Complications

Post-stroke and post-procedural complications were compared between dichotomized sedation groups as above, and are presented in Table 3. We found a significantly higher rate of pneumonia and/or sepsis in patients receiving heavy sedation or pharmacologic paralysis (p=0.02). There were highly non-significant trends toward more symptomatic and asymptomatic hemorrhages and fewer access site related complications in the groups receiving heavy sedation or paralysis.

Discussion

To our knowledge, our report is the first formal examination of the issue of procedural sedation and intubation within a controlled acute interventional ischemic stroke trial. Our data adds to considerable discussion in the literature regarding the potential beneficial and untoward effects of sedative medications on patient outcome and stroke recovery. In particular, the intensive care and anesthesia literatures have shown that continuous use of sedative medications prolongs intubation time and lengthens ICU stays.[8,9] Continuous sedation has also been associated with an increased likelihood of developing pneumonia in intubated patients.[10] Conversely, the potential neuroprotective benefits of some sedative medications have been investigated for years, though have never been proven to be of benefit in acute stroke.[11,12,13]

Our goal was to clarify the factors that were associated with the use of higher levels of sedation in patients undergoing angiography. Further, we wanted to discern the association, if any, between the use of sedation and clinical outcomes and the ability to obtain successful reperfusion. Our analysis shows that higher baseline NIHSS scores correlated with use of deeper sedation during or prior to angiography and/or intervention. Heavily sedated patients were also significantly less likely to obtain successful angiographic reperfusion as measured by post-treatment TIMI scores, a finding that is perhaps related to higher rates of ICA occlusions and associated with longer procedural durations. From a clinical standpoint, it is not surprising that we found that patients with the lowest levels of sedation fared better.

We are unable to conclude whether sedation is a cause of poor outcome due to causing increased complications or impairing recovery or whether patients with large strokes, as measured by higher baseline NIHSS, are more likely to be sedated. It is clear that patients with higher baseline NIHSS have poorer clinical outcome, higher morbidity and mortality and greater rates of symptomatic ICH. However, sedation category remained a predictor of poor outcome and death when baseline NIHSS score was accounted for in multivariable analysis. It remains possible, therefore, that the use of sedation itself is related to clinical outcome, given our findings. Alternatively, it is also possible that the use of heavier sedation is a non-specific marker for a group of unmeasured clinical factors that predict poor outcome.

From a procedural standpoint, there was a non-significantly lower rate of access site-related complications associated with heavier sedation. Whether this difference is found to be significant in additional studies remains to be seen. In this analysis, access site-related complications were limited to groin hematomas, a single arterial pseudoaneurysm, a moderate severity common iliac occlusion, and/or local bleeding. There were no significant retroperitoneal hemorrhages in this cohort. In practice, the vast majority of the above access site-related complications can be treated by manual compression or conservative measures. Based on our analysis, we suggest that reducing the rate of access site-related complications should not influence neurointerventional specialists to heavily sedate or pharmacologically paralyze their patients alone.

Conversely, heavy sedation or paralysis may be warranted if patient movement is felt to pose an increased risk of vessel perforation or dissection. In this analysis, the only vessel dissection occurred in a cervical carotid artery in a patient in the heavily sedated group. Whether patient agitation or movement may have contributed to dissection is unknown. Because these complications are rare, however, we are unable to conclude whether greater sedation or paralysis is useful in avoiding these complications.

We did find a significantly higher rate of infection in those patients receiving heavy sedation or pharmacological paralysis. Whether short-term or long-term use of sedative medications is in part responsible for higher infection rates in those patients is unclear based on this analysis. However, given these findings, we cannot overlook the fact that medication effects may play some role in immunosuppression, aspiration risk, or prolongation of intubation time.

This analysis is limited by its small sample size. While we were able to demonstrate a significant association between sedation and outcome, the magnitude of that association is unclear, as evidenced by the wide confidence intervals around the odds ratios. In a larger population, we might be able to conclude whether sedation alone appears to influence outcome. Our inability to precisely determine the types of medications, their duration of use, or the route of administration in each case also limits this analysis. While we did record all medications used as part of the study, the times of administration with respect to the angiographic procedure were not recorded, nor was their duration of use.

Conclusion

In this study, we characterize the wide variability in the use of sedation in patients undergoing intra-arterial therapy. Initial stroke severity, as measured by the NIHSS score, was highly associated with the use of deeper sedation. Further, the use of sedation was a more potent marker for poor outcome and death than the initial NIHSS score. Additional study is needed to determine if higher levels of sedation simply mark patients with a poorer outcome, or if they impair stroke recovery and lead to iatrogenic complications, as represented by higher infection rates in this analysis.

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Table 1

Characteristics of patients in each sedation category*

	No Sedation (n=40)	Mild Sedation (n=9)	Heavy Sedation (n=9)	Pharmacological Paralysis (n=17)	All Groups (n=75)	p-value**
Age	64.6 ± 11.4	63.6 ± 10.3	64.0 ± 12.2	62.8 ± 12.6	64.0 ± 11.5	0.98
Baseline NIHSS	17.3 ± 4.5	19.4 ± 8.3	21.0 ± 5.5	21.2 ± 4.0	18.9 ± 5.3	0.03
Male Gender	26 (65.0%)	4 (44.4%)	3 (33.3%)	11 (64.7%)	44 (58.7%)	0.26
Non-White	7 (17.5%)	2 (22.2%)	1 (11.1%)	5 (29.4%)	15 (20.0%)	0.68
Atrial Fibrillation	11 (27.5%)	2 (22.2%)	2 (22.2%)	3 (17.7%)	18 (24.3%)	0.95
Baseline Glucose	120.1 ± 42.6	116.1 ± 19.4	169.0 ± 104.2	125.2 ± 38.8	126.6 ± 52.5	0.68
Baseline SBP	143.8 ± 22.6	150.1 ± 10.4	143.7 ± 20.9	147.4 ± 21.0	145.4 ± 20.7	0.83
Left Hemisphere Involved	20 (50.0%)	6 (66.7%)	8 (88.9%)	11 (64.7%)	45 (60.0%)	0.17
Aphasia Present	19 (47.5%)	6 (66.7%)	8 (88.9%)	11(64.7%)	44 (58.7%)	0.11
ICAT occlusion	7 (18.4)	1 (11.1)	2 (22.2)	8 (47.1)	18 (24.7)	0.12
Onset to IV treatment (min)	141.6 ± 33.5	127.7 ± 38.3	139.1 ± 28.4	139.0 ± 25.5	139.1 ± 31.6	0.75
Received IA treatment	25 (62.5%)	8 (88.9%)	8 (88.9%)	12 (70.6%)	53 (70.7%)	0.31
Onset to IA treatment (min)	231.6 ± 55.3	234.6 ± 55.0	238.5 ± 35.4	236.8 ± 57.7	234.3 ± 51.9	0.99
Duration of procedure (min)	111.2 ± 59.3	119.9 ± 65.9	150.9 ± 44.4	136.8 ± 65.7	123.1 ± 60.5	0.26

* Categorical variables are described using n (%), and continuous variables are presented as mean ± standard deviation

** P-values represent variation across all 4 sedation categories.

Table 2

Outcomes in patients receiving different levels of sedation.

	No Sedation	Mild Sedation	Heavy Sedation	Pharmacological Paralysis	All Groups	p- value*
	(n=40)	(n=9)	(n=9)	(n=17)	(n=75)	
Death	3 (7.5%)	1 (11.1%)	2 (22.2%)	6 (35.2%)	12 (16%)	0.02
	4 (8.2%)		8 (30.8%)			
mRS 0–2	24 (60%)	6 (66.6%)	2 (22.2%)	4 (23.5%)	36 (48%)	<0.01
	30 (61.2%)		6 (23.1%)			
Successful Reperfusion (TIMI 2–3)	24/33 (72.7%)		7/20 (35%)		31/53 (58.5%)	0.01

* p-values represent dichotomized sedation categories

Table 3

Complications in patients receiving different levels of sedation.

	None or Mild Sedation (n=49)	Heavy Sedation or Paralyzed (n=26)	p-value
Intracerebral hemorrhage			
Symptomatic	4 (8.2%)	5 (19.2%)	0.26
Asymptomatic	7 (14.3%)	9 (34.6%)	0.07
Infections	4 (8.2%)	8 (30.8%)	0.02
Access site related complications	12 (24.5%)	4 (15.4%)	0.55
Vessel dissection or perforation	0	1 (3.9%)	0.35
Acute MI	2 (4.1%)	1 (3.9%)	1