Do stress markers and anesthetic technique predict delirium in the elderly?

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Abstract

Background—Postoperative delirium (PD) is a prevalent complication of elderly surgical patients which predisposes toward worsened cognitive recovery and dementia. Risk of PD has been associated with increasing magnitude of the hypothalamic-pituitary-adrenal stress response (serum cortisol, epinephrine, norepinephrine) to surgery. Anesthetics suppress this response, some (total intravenous anesthesia, TIVA) more than others (anesthetic gases). Prior comparisons of anesthetics have been equivocal but have not included stress markers. We hypothesized that TIVA would decrease serum stress markers and the incidence of PD.

Methods—We performed a prospective cohort study of 76 elderly major surgical patients. Patients received TIVA or sevoflurane gas, blood was drawn for serum markers pre-, intra-, and postoperatively. PD was assessed with the Confusion Assessment Method. We compared stress markers and PD between patients who had TIVA vs. sevoflurane, then modeled PD including stress and anesthetic.

Results—The group that received TIVA during surgery demonstrated lower levels of all stress markers compared to the gas group, but no difference in PD. However, across groups, postoperative norepinephrine was much higher in patients who developed PD. Other markers and other times had no effect.

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Conclusion—The development of PD depends more on postoperative stress than intraoperative stress or anesthetic.

One of the most prevalent and morbid complications for elderly surgical patients is postoperative delirium (PD). This acute confusional state occurs hours to days after surgery in 15–53% of patients and associated with worsened cognitive recovery after illness and long term cognitive impairment and increased risk of dementia (1–7). PD is responsible for longer hospital stays and greater median hospital costs estimated at 6.9 billion dollars of additional Medicare expenditures every year (8–10). Anesthesia and choice of anesthetic medications are an intuitive culprit, however there have been a limited number of studies comparing delirium incidence between anesthetic medications with very limited common ground between them (11). Hence equipoise remains regarding whether delirium and other neurocognitive outcomes differ by choice of anesthetic drug (12).

Anesthetic could have a direct impact on the incidence of delirium based on the theory that PD may be a "sickness behavior" resulting from an extreme manifestation of the stress response to surgery as mediated by the hypothalamic pituitary adrenal (HPA) including serum cortisol, epinephrine, and norepinephrine (13, 14). While there is data to suggest that hyperresponsiveness of the HPA axis is associated with PD in elderly surgical patients, there has been no direct comparison of anesthetic agents and their ability to reduce the stress response and PD (15).

All anesthetics suppress the stress response to surgery; however some more completely than others (16). Anesthetic gases only mildly suppress the cortisol response to surgery; but total intravenous anesthesia with propofol (TIVA) significantly blunts the cortisol response and production of catecholamines (17, 18) . However, this information has been generalized from younger patients; the difference in stress response between anesthetic medications and delirium in the elderly has not been studied.

A randomized trial of TIVA vs. gas is difficult due to the constraints of surgery (e.g. spine surgery requiring neuromonitoring). To directly investigate anesthetic choice, stress response, and incidence of postoperative delirium we performed a prospective cohort study and hypothesized that elderly surgical patients who received TIVA would have lower serum markers of stress than those receiving gas and therefore have a lower incidence of PD as measured by the Confusion Assessment Method (CAM) (19). Then in posthoc analysis we modeled the outcome of PD adjusted for both the stress response and anesthetic to identify risk factors for the elderly surgical patients.

Methods

With IRB approval and informed consent we performed a prospective study of patients over age 68 scheduled for major non-cardiac surgery under general anesthesia including general, spine, urologic, or thoracic surgery at the Mount Sinai Hospital NY, NY. Major surgery was defined as planned hospital stay of at least 2 days. Exclusion criteria included intracranial surgery, cardiac surgery, preexisting neuropsychiatric disease, history of CVA with residual deficits, baseline Mini-Mental Status Exam (MMSE) < 20 or unable to consent for study

participation, and/or unable to speak English. Eligible patients were identified using the computerized scheduling system and approached by phone at least 24 hours prior to surgery.

Seventy–six patients consented and completed the in-hospital portion of the protocol. The medical history was obtained from the patient and confirmed with the anesthesiologist at the time of surgery. Patients were given a 1 hour assessment prior to the day of surgery but within 30 days including neuropsychological battery, Mini Mental Status Exam (MMSE), and CAM assessment (20)(19). Demographics and medical history were collected from patient interviews, and medical record confirmed from presurgical exam completed by a physician (coronary artery disease, diabetes, hypertension, malignancy, renal disease, respiratory disease, history of TIA/stroke). American Society of Anesthesiology Physical Status (ASA), a classification of physical status, where ASA 1 is healthy, ASA 2 signifies mild disease, ASA 3 is systemic disease which limits function, ASA 4 disease which is a constant threat to life, and ASA 5, not expected to survive as determined by the anesthesiologist. Intraoperative data collected included vital signs, estimated blood loss (EBL), anesthetic, surgery type, and the surgery duration (Table 2). On the day of surgery, patients had blood drawn for stress markers: cortisol, epinephrine, norepinephrine immediately prior to surgery, 4 hours after surgery started, and at 2 hours after surgery.

Patients received either TIVA consisting of propofol infusion or gas (sevoflurane). The choice of gas vs. TIVA anesthetic was determined by the clinical anesthesia team based on requirements for the procedure. The anesthesia team was instructed to avoid benzodiazepines and nitrous oxide but permitted to choose any induction agent, and narcotic, or paralytic. Patients were seen by the research team and assessed with the CAM and MMSE in the recovery room ("delirium in PACU" or emergence delirium) and on each postoperative day ("delirium postop day", postoperative delirium).

Statistical analysis

The Chi Squared test or Fisher's Exact test for categorical variables, and Students t-test or Wilcoxon rank sum test for continuous variables were used to compare the TIVA and gas groups at baseline, with respect to intraoperative variables, and the incidence of PD. These analytic methods were also applied to the post-hoc analysis to compare patients who did and did not develop postoperative delirium (PD+) (Table 3). Variables associated with PD+ with a p-value < 0.2 in univariate analysis and/or of clinical significance were used to fit a forward stepwise logistic regression model of delirium which developed in the postoperative days. A receiver-operator curve was generated to demonstrate prediction ability, and the Pearson Goodness of Fit test was used to demonstrate model fit. Model coefficients, odds ratios and the corresponding 95% confidence intervals are listed in Table 4.

Because of the very broad range of delirium in previous studies which have been heterogeneous with respect to surgical population and agents, and the diurnal variation of cortisol, sample size for this study was based on the difference in norepinephrine response between the gas and TIVA groups which has been better characterized. For this purpose we used the difference in serum norepinephrine levels between groups from the work of Marana et al which showed a 300 pg/ml difference between patients who received gas and those who

received TIVA. (17). With a sample size of 75 using a 2-sided 0.05 t-test, we would have greater than 80% power to detect a difference of this magnitude.

Results

Table 1 compares the TIVA and gas groups on baseline clinical and demographic variables. The TIVA group was younger (73.48 vs. 76.33, p= .024), had a higher baseline MMSE score (29 vs. 27 p = .029), and lower ASA physical status indicating less comorbid disease (p= .021). Table 2 compares intraoperative and postoperative independent variables between the TIVA and gas groups. Median EBL was higher in the TIVA group (375 vs. 200ml, p= .029); anesthesia and surgical times were similar between both groups. Median postoperative pain scores as measured by the visual analog score (VAS) were similar in both groups in the recovery room. Cortisol was higher in the gas group at all time points (p=.002, p<.001, p<.001). Serum epinephrine and norepinephrine were similar at baseline and lower in the TIVA group during and after surgery. Despite the fact that the TIVA group was younger and had better baseline cognition, the incidence of immediate postoperative delirium was not different between the two groups in the postoperative care unit (PACU) (gas3.2% vs. TIVA 7.5% p= .622) nor on the postoperative days (gas 22.2% vs. TIVA 15% p=.417).

Table 3 compares patients who did and did not develop PD on postoperative days 1–3. Recovery room level of norepinephrine (p=.03) was much higher in patients who developed PD, with no significant difference in intraoperative levels of norepinephrine, cortisol or epinephrine levels. There was a trend toward an association between lower baseline MMSE (p=.056) and higher ASA physical status indicating a sicker patient (p=.083), and preexisting diabetes (p=.156); these were included in the multivariable analysis. A larger proportion of patients who had delirium in the recovery room (22.2% vs. 3.4%) went on to have delirium in the postoperative days, but this result was not significant (p=.084). Duration of surgery (p=.097) was marginally associated with development of PD but anesthetic group, EBL, type of surgery and anesthesia duration were not associated with delirium.

Table 4 describes the multivariable stepwise logistic regression which models the outcome of PD including variables with univariate association (p<.2) and clinical significance. In this model the predictors which remained in the model were DM, surgical duration, and the postoperative level of NE (Table 3). Diabetics had 4.51 times the odds of developing PD (95% CI 1.00–20.14). For every 100 pg increase in serum norepinephrine the odds of PD increased by approximately 20% (95% CI 1.01–1.42). Surgical duration was a marginal predictor, for every 1 hour increase the odds of PD increased 1.46 times (95% CI .92–2.32). In a model which included these three variables, serum glucose, PACU delirium, surgical procedure, ASA, EBL, and MMSE were not significant. The area under the receiver operator curve for this model was 0.772 (Figure 1).

Discussion

In this study, there was no significant difference in the incidence of PD between elderly patients who received TIVA and gas; however the TIVA group demonstrated suppression of

norepinephrine, epinephrine, and cortisol during surgery. The recovery room level of serum norepinephrine was predictive of delirium and the median recovery room norepinephrine levels of patients who became delirious were higher than during surgery in any group. This suggests that the magnitude of the stress response which may be quite high in the recovery room due to hypothermia, anxiety, and pain is more important than anesthetic technique in the development of PD.

Our finding of the relationship between stress and delirium may have particular relevance for the elderly; animal studies suggest that increased age is associated with prolonged stress response to systemic inflammation and longer lasting cognitive impairment (21, 22). Mechanistically, serum norepinephrine is associated with neuronal injury and worsened delirium and prior studies suggest that alpha adrenergic blocking sedatives (dexmedetomidine) may decrease delirium in the ICU(23) (24)(1). In our study serum epinephrine and cortisol were not different between patients who did and did not develop PD. These results are consistent with other studies which show that the magnitude of the cortisol, epinephrine, and norepinephrine response are not entirely parallel (17).

While the recovery room level of serum norepinephrine response was important in our model, it was not the sole determining factor for development of PD. Our multivariable model suggests that PD is the result of a more complicated interaction between stress and the underlying patient characteristic of diabetes. This suggests that preexisting vulnerability (e.g. diabetes) predispose certain patients to delirium. The impact of diabetes is much broader than its effect on glycemic control; in our study we did examine serum glucose (not shown) which was higher mildly in patients with PD but was not an independent predictor of PD. One possible mechanism by which diabetes may contribute to delirium aside from acute glycemic control includes its effects on the blood brain barrier (BBB) (25). Previous studies have shown that the BBB exhibits structural and functional changes with age and pathological conditions e.g. Type II Diabetes (26, 27). Systemic mediators such as serum norepinephrine have been shown to influence the central nervous system milieu through indirectly by activating endothelial cells of the brain's vasculature to secrete prostaglandins or stimulate afferents of the vagus nerve which stimulate the nucleus tractus solitaries (24, 28).

In both TIVA and gas groups the incidence of delirium that we found was within the range described for older general surgery patients. The magnitude of the difference between groups is similar to that observed by Royce et al. but much larger than found by T. Monk et al. in elderly patients having hip surgery (29). Because this was not a randomized study there were some important differences between the TIVA and gas groups which may have influenced this including that the TIVA group was approximately 3 years younger, had a somewhat higher baseline MMSE, and had lower ASA status (less comorbidity burden) than the gas group. These factors would also seem potential driving factors for the outcome of delirium. However, in a multivariable model adjusted for the presence of diabetes, surgical duration, and serum norepinephrine in the recovery room, the baseline features of age, MMSE, and ASA status were not significant.

Limitations

This study was underpowered to observe a difference in incidence of delirium between the TIVA and gas groups. Based on the observed 7% difference between the groups we would have needed 953 patients (476 in each arm) to have achieved statistical significance. Whether this difference is clinically meaningful and worth further prospective study is questionable. The anesthetic was standardized but the patients were not randomized to TIVA or gas because many were restricted to a group based on the surgery. For example, patients undergoing spine surgery often require neuromonitoring which is facilitated by the use of TIVA. However, there was no difference in the distribution of surgical procedures between patients who did and did not develop delirium.

While there were some baseline differences between the group (age, ASA status) we were able to measure and adjust for these. We also adjusted for surgical procedure, estimated blood loss and comorbidity.

Conclusion

In this study we did not observe a clear association between anesthetic technique and either emergence delirium or postoperative delirium. We have found that the recovery room level of norepinephrine is much higher than during surgery and is a risk factor for postoperative delirium. Our findings suggest a complex interplay between the stress response in vulnerable elderly patients especially those with diabetes. We hope that presentation of this data will refocus the study of postoperative delirium to include the immediate postoperative period which has not traditionally focused on the geriatric patient and has several areas amenable to improvement (postoperative pain control, anxiety, temperature regulation). Given the evidence that delirium is associated with long term cognitive sequelae and dementia, studies of the cognitive health and recovery of postsurgical elderly patients should focus on the postoperative period. Future studies should investigate the immediate postoperative period to identify strategies to prevent or mitigate postoperative delirium.

Acknowledgments

References

1. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. JAMA. 2007 Dec 12; 298(22):2644–53. [PubMed: 18073360]

2. Davis DH, Muniz Terrera G, Keage H, Rahkonen T, Oinas M, Matthews FE, et al. Delirium is a strong risk factor for dementia in the oldest-old: A population-based cohort study. Brain. 2012 Sep; 135(Pt 9):2809–16. [PubMed: 22879644]

3. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: A meta-analysis. JAMA. 2010 Jul 28; 304(4):443–51. [PubMed: 20664045]

4. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med. 2010 Jul; 38(7):1513–20. [PubMed: 20473145]

5. Verloo H, Goulet C, Morin D, von Gunten A. Delirium among home-dwelling elderly after a recent hospitalization: An urgent need for effective nursing interventions. Dement Geriatr Cogn Dis Extra. 2012 Jan.2:187–9. [PubMed: 22719744]

6. Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Prognostic significance of delirium in frail older people. Dement Geriatr Cogn Disord. 2005; 19(2–3):158–63. [PubMed: 15627764]

7. Silverstein JH, Deiner SG. Perioperative delirium and its relationship to dementia. Prog Neuropsychopharmacol Biol Psychiatry. 2013 Jun 3.43:108–15. [PubMed: 23220565]

8. Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. Br J Anaesth. 2009 Dec; 103(Suppl 1):i41–46. [PubMed: 20007989]

9. Franco K, Litaker D, Locala J, Bronson D. The cost of delirium in the surgical patient. Psychosomatics. 2001; 42(1):68–73. [PubMed: 11161124]

10. Inouye SK. Delirium in older persons. N Engl J Med. 2006 Mar 16; 354(11):1157–65. [PubMed: 16540616]

11. Zhang H, Lu Y, Liu M, Zou Z, Wang L, Xu FY, et al. Strategies for prevention of postoperative delirium: A systematic review and meta-analysis of randomized trials. Crit Care. 2013 Mar 18.17(2):R47. [PubMed: 23506796]

12. Royse CF, Andrews DT, Newman SN, Stygall J, Williams Z, Pang J, et al. The influence of propofol or desflurane on postoperative cognitive dysfunction in patients undergoing coronary artery bypass surgery. Anaesthesia. 2011 Jun; 66(6):455–64. [PubMed: 21501129]

13. MacLullich AMJ, Ferguson KJ, Miller T, de Rooij SEJA, Cunningham C. Unravelling the pathophysiology of delirium: A focus on the role of aberrant stress responses. J Psychosom Res. 2008 Sep; 65(3):229–38. [PubMed: 18707945]

14. Hall RJ, Shenkin SD, Maclullich AM. A systematic literature review of cerebrospinal fluid biomarkers in delirium. Dement Geriatr Cogn Disord. 2011; 32(2):79–93. [PubMed: 21876357]

15. Cerejeira J, Batista P, Nogueira V, Vaz-Serra A, Mukaetova-Ladinska EB. The stress response to surgery and postoperative delirium: Evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased suppression of the GH/IGF-1 axis. J Geriatr Psychiatry Neurol. 2013 Sep; 26(3):185–94. [PubMed: 23864592]

16. Roizen MF, Horrigan RW, Frazer BM. Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision--MAC BAR. Anesthesiology. 1981 May; 54(5):390–8. [PubMed: 7224208]

17. Marana E, Colicci S, Meo F, Marana R, Proietti R. Neuroendocrine stress response in gynecological laparoscopy: TIVA with propofol versus sevoflurane anesthesia. J Clin Anesth. 2010 Jun; 22(4):250–5. [PubMed: 20522354]

18. Ledowski T, Bein B, Hanss R, Paris A, Fudickar W, Scholz J, et al. Neuroendocrine stress response and heart rate variability: A comparison of total intravenous versus balanced anesthesia. Anesth Analg. 2005 Dec; 101(6):1700–5. [PubMed: 16301244]

19. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990 Dec 15; 113(12):941–8. [PubMed: 2240918]

20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov; 12(3):189–98. [PubMed: 1202204]

21. Chapman TR, Barrientos RM, Ahrendsen JT, Maier SF, Patterson SL. Synaptic correlates of increased cognitive vulnerability with aging: Peripheral immune challenge and aging interact to disrupt theta-burst late-phase long-term potentiation in hippocampal area CA1. J Neurosci. 2010 Jun 2; 30(22):7598–603. [PubMed: 20519534]

22. Barrientos RM, Frank MG, Hein AM, Higgins EA, Watkins LR, Rudy JW, et al. Time course of hippocampal IL-1 beta and memory consolidation impairments in aging rats following peripheral infection. Brain Behav Immun. 2009 Jan; 23(1):46–54. [PubMed: 18664380]

23. Bhardwaj A, Brannan T, Martinez-Tica J, Weinberger J. Ischemia in the dorsal hippocampus is associated with acute extracellular release of dopamine and norepinephrine. J Neural Transm Gen Sect. 1990; 80(3):195–201. [PubMed: 2331346]

24. Maldonado JR. Neuropathogenesis of delirium: Review of current etiologic theories and common pathways. Am J Geriatr Psychiatry. 2013 Dec; 21(12):1190–222. [PubMed: 24206937]

25. Hughes CG, Morandi A, Girard TD, Riedel B, Thompson JL, Shintani AK, et al. Association between endothelial dysfunction and acute brain dysfunction during critical illness. Anesthesiology. 2013 Mar; 118(3):631–9. [PubMed: 23263016]

26. Mooradian AD. Potential mechanisms of the age-related changes in the blood-brain barrier. Neurobiol Aging. 1994 Nov-Dec;15(6):751,5. discussion 761–2, 767. [PubMed: 7891831]

27. Starr JM, Wardlaw J, Ferguson K, MacLullich A, Deary IJ, Marshall I. Increased blood-brain barrier permeability in type II diabetes demonstrated by gadolinium magnetic resonance imaging. J Neurol Neurosurg Psychiatry. 2003 Jan; 74(1):70–6. [PubMed: 12486269]

28. Uchikado H, Akiyama H, Kondo H, Ikeda K, Tsuchiya K, Kato M, et al. Activation of vascular endothelial cells and perivascular cells by systemic inflammation-an immunohistochemical study of postmortem human brain tissues. Acta Neuropathol. 2004 Apr; 107(4):341–51. [PubMed: 14762673]

29. Study finds that anesthetics do not cause postoperative delirium in the elderly [Internet]. 2011. Available from: http://www.asahq.org/Home/For%20the%20Public%20and%20Media/Press%20Room/Anesthesiology%20and%20Other%20Scientific%20Press%20Releases/Study%20Finds%20That%20Anesthetics%20Do%20Not%20Cause%20Postoperative%20Delirium%20in%20the%20Elderly.aspx

Table 1

Baseline comparison of the GAS vs. TIVA groups

		GAS N=36	TIVA N=40	p value
Age		76.33(5.75)	73.48(5.03)	0.024
Gender	Female	21 (58.3%)	19 (47.5%)	0.345
	Male	15 (41.7%)	21 (52.5%)	
ASA status	1	1(2.78%)	0 (0%)	
	2	3(8.33%)	15(37.5%)	0.021
	3	26(72.22%)	21(52.5%)	
	4	6 (16.67%)	4(10.0%)	
CAD		7(19.4%)	5(12.5%)	0.407
CVA		1(2.8%)	4(10.0%)	0.362
Diabetes		8(22.2%)	8(20.0%)	1.000
Malignancy		25(69.4%)	11(28.2%)	<0.001
Renal		4(11.1%)	3(7.5%)	0.702
Surgery	Spine	1(2.78%)	36(90%)	<.0001
	Urology	7(19.44%)	2(5%)	
	General	20(55.56%)	2(5%)	
	Thoracic	8(22.22%)	0 (0%)	
Preoperative MMSE		27 [26–30]	29 [28–30]	0.029

Data are presented as mean (SD), median [25th percentile, 75th percentile], or N (%). The tests for group comparisons are 2-sample t-test, Wilcoxon rank sum test, Chi-square test or Fisher's exact test, as appropriate.

Table 2

Comparison of the GAS vs. TIVA groups

		GAS N=36	TIVA N=40	p value
MMSE	Baseline	27 [26–30]	29 [28–30]	0.029
EBL		200 [100–500]	375 [200–750]	0.029
Surgery Duration		167 [127–231]	190 [146–254]	0.147
Anesthesia Duration		263 [236–314]	270 [231–357]	0.579
VAS in recovery room		7 [5–9]	7[5–9]	0.962
Cortisol	Baseline	12.45 [8.80–19.15]	9.65 [5.75–12.25]	0.002
	Intraop	31.8 [14.55–38.60]	4.8 [2.90–9.60]	<.001
	Recovery	31.35 [18.45–45.80]	13.4 [3.40–17.70]	<.001
Epinephrine	Baseline	39 [0–62]	23 [0–41]	0.085
	Intraop	65 [25–170]	0 [0–53]	<.001
	Recovery	127 [57–215]	57 [0–98]	0.004
Norepinephrine	Baseline	278 [138–480]	361 [202–502]	0.410
	Intraop	341[150–597]	136 [90–266]	<.001
	Recovery	434 [199–811]	311 [162–467]	0.107
Delirium in PACU		1 (3.2%)	3 (7.5%)	0.622
Delirium Postop day		8 (22.2%)	6(15%)	0.417

Data are presented as mean (SD), median [25th percentile, 75th percentile], or N (%). The tests for group comparisons are 2-sample t-test, Wilcoxon rank sum test, Chi-square test or Fisher's exact test, as appropriate. MMSE: Minimental Status, EBL: estimated blood loss, VAS: visual analog score for pain in the recovery room. Cortisol (mcg/dl), Epinephrine (pg/ml), Norepinephrine (pg/ml) : serum levels at baseline= immediately prior to surgery, Intraop= 4 hours after surgical start Recovery= 2 hours after surgery finish

Table 3

Comparison of patients who did (PD+) and did not (PD-) develop delirium

		PD(−) N=62	PD(+) N=14	p value
Age		73.48(5.03)	75.83(5.41)	
Gender	Male	30 (48.4%)	10 (71.4%)	0.146
	Female	32 (51.6%)	4 (28.6%)	
ASA Status	1	0 (0%)	1 (7.1%)	
	2	17 (27.4%)	1 (7.1%)	0.083
	3	37 (59.7%)	10 (71.4%)	
	4	8 (12.9%)	2 (14.3%)	
CAD		8 (11.9%)	4 (28.6%)	0.217
CVA		4 (6.5%)	1 (7.1%)	1.000
Diabetes		11 (17.7%)	5 (35.7%)	0.156
Glucose	Baseline	94 [85–106]	103 [81–118]-	0.439
	Intraop	116 [96–142]	143 [101–152]	0.121
	Recovery	127 [107–149]	167 [117–187]	0.055
Malignancy		30 (49.2%)	6 (42.9%)	0.771
Renal		6 (9.7%)	1 (7.1%)	1.000
Anesthesia				
	Gas	28(77.8%)	8(22.2%)	.417
	TIVA	34(85%)	6(15%)	
Surgery	Spine	31 (50%)	6 (42.9%)	0.621
	Urology	8 (12.9%)	1 (7.1%)	
	General	16 (25.8%)	6 (42.9%)	
	Thoracic	7 (11.3%)	1 (7.1%)	
MMSE	Baseline	29 [27–30]	27 [25–29]	0.056
EBL		250 [100–600]	200 [150–700]	0.761
Surgery Duration		171 [136–246]	191 [168–239]	0.097
Anesthesia Duration		266 [230–316]	288 [256–359]	0.119
VAS in recovery		7[5–9]	7[6–10]	0.350
Cortisol	Baseline	11.25 [8.1–13.9]	9.3[5.3–11.7]	0.178
	Intraop	13.6 [4.8–32.3]	10.5 [3.3–31.3]	0.740
	Recovery	18.8 [8.3–33.2]	14.6 [12.6–31.7]	0.978
Epinephrine	Baseline	26 [0–54]	14.5 [0–50]	0.746
	Intraop	35 [0–78]	36 [0–170]	0.588
	Recovery	76 [39–145]	131 [48–196]	0.388
Norepinephrine	Baseline	296 [174–480]	419 [278–495]	0.556
	Intraop	185 [109–341]	300 [68–597]	0.314
	Recovery	322 [150–541]	586 [346–811]	0.030
PACU delirium		2 (3.4%)	2 (22.2%)	0.084

Data are presented as mean (SD), median [25th percentile, 75th percentile], or N (%). The tests for group comparisons are 2-sample t-test, Wilcoxon rank sum test, Chi-square test or Fisher's exact test, as appropriate. MMSE: Minimental Status, EBL: estimated blood loss, VAS: visual

analog score for pain in the recovery room. Cortisol(mcg/dl), Epinephrine (pg/ml), Norepinephrine (pg/ml), Glucose (mg/dl): serum levels, at baseline= immediately prior to surgery, Intraop= 4 hours after surgical start Recovery= 2 hours after surgery finish

Table 4

Multivariable Logistic Model of Delirium

Predictor	Unit	Odds Ratio	95% CI
Surgical Duration	1 hour	1.46	0.92–2.32
Recovery Room Norepinephrine level	100 pg/ml	1.20	1.01–1.42
Diabetes	1= yes	4.51	1.01–20.14