Date: February 20, 2017
Version Number: 11
Principal Investigator: Quinn Johnson, MD
Application Number: 1212915
Application Title:

Does Optimized General Anesthesia Care Reduce Postoperative Delirium In Older Patients Undergoing Hip Fracture Repair?

Protocol

****

1. Abstract

The overall objective of this proposal is to determine if optimized general anesthesia care of elderly patients undergoing hip fracture surgery will minimize postoperative delirium (POD) and improve postoperative outcomes. A proactive geriatric consultation using a multifactorial bundle of pharmacological and non-pharmacological strategies in the perioperative period has been shown to effectively reduce POD, but even with these perioperative medical interventions, more than 30% of patients undergoing hip fracture surgery experience POD.[1,2]

There is tantalizing preliminary evidence suggesting that intraoperative interventions may also have the potential to further decrease POD. [3-6] This prospective randomized clinical trial (RCT) will focus on the intraoperative optimization of: 1. blood pressure, 2. depth of anesthesia, 3. cerebral oxygenation, and 4. postoperative pain management in an effort to further reduce POD. All of these interventions can easily be managed by anesthesia providers during surgery. A total of 160 patients will be randomized to optimal versus usual anesthesia care for hip fracture surgery to determine the impact of this targeted anesthesia care bundle on the severity and incidence of POD. The results of our proposed study are intended to enhance patient safety by developing a relatively easily implemented, generalizable anesthesia management strategy that can be used by anesthesia providers in both academic and private settings. This proposal has the potential to further reduce POD, thereby decreasing patient morbidity and mortality.

2. Objectives (include all primary and secondary objectives)

The primary objective of this proposal is to develop an optimized general anesthetic plan, focusing on anesthetic depth, blood pressure control, and cerebral oxygenation for elders undergoing hip fracture surgery. This protocol will compare usual care to optimal general anesthesia care to test the following **hypotheses**:

The use of an optimized general anesthetic technique for elders undergoing hip fracture surgery will:

- **Primary hypothesis: decrease the severity of POD**
- **Secondary hypothesis 1: decrease the incidence and duration of POD**
- **Secondary hypothesis 2: decrease the length of stay in the hospital**
- **Secondary hypothesis 3: to determine if poor performance on preoperative cognitive tests or preoperative depression identify patients at high-risk for POD**
- **Secondary hypothesis 4: to determine if the level of preoperative inflammation predicts patients at risk for POD**

3. Background

Postoperative delirium (POD) is common in elderly patients and is reported to occur in 35 to 65% of patients undergoing hip fracture surgery.[8] Despite the fact that delirium is a temporary condition, it is a medical and societal stressor from an economic and healthcare standpoint. POD is independently associated with increased morbidity, mortality, length of hospital stay, and placement in long-term care institutions. It increases the cost of hospitalization by $4000 for each patient who develops this complication and the total costs attributed to the treatment of delirium in the US are estimated to be as high as $152 billion each year.[9,10]

The etiology of POD is multifactorial and involves a complex interaction between a vulnerable patient with preoperative risk factors who is exposed to numerous ***precipitating factors in the perioperative period***.[11] Most of the preoperative risk factors such as age, comorbidities and cognitive status are fixed and cannot be modified during the perioperative period. However, there are perioperative factors that are directly under the control of the anesthesia provider that could potentially be modified to minimize POD.

At the present time, only multi-component medical interventions have shown to consistently reduce POD.[1,12,13] Although it makes sense that neuraxial anesthesia would be associated with less POD than general anesthesia (GA), there is no evidence to support this theory, possibly because sedation levels were not controlled in these studies.[14] There is, however, limited evidence that minimizing anesthetic exposure during hip fracture surgery might decrease POD. Sieber et al.[3] randomized elderly patients undergoing hip fracture repair with spinal anesthesia to light versus deep propofol sedation for the procedure and found that light propofol sedation (BIS > 80) decreased the incidence of POD by 50% compared with deep sedation (BIS =50). Despite the promising results of this study, the study results have been questioned because the two treatment groups were not matched with respect to cognitive and functional status.[12] A more important issue is that spinal anesthesia is rarely used for patients undergoing hip fracture surgery. A large retrospective study of 56,729 patients having hip fracture surgery in the US found that only 28% of patients received regional anesthesia and that GA was much more common (72%).[15] There are a multitude of reasons that anesthesia providers prefer to administer GA for hip fracture surgery including patient preference, avoidance of pain during positioning of the patient, difficulty with block placement in elderly patients with arthritic spines, and the use of anticoagulation in many elders. An optimized general anesthetic technique is, therefore, needed to improve postoperative outcomes in elders receiving GA for this hip fracture surgery.

Modifiable Intraoperative Factors

There is growing evidence that limiting the amount of anesthesia during GA may decrease the incidence of POD. Chan et al.[5] prospectively randomized elderly patients undergoing elective major surgery to either BIS-guided or routine care anesthesia and found that patients in the BIS-guided group received less anesthetic and had a 35% decrease in the incidence of POD. A second prospective study randomized elders undergoing elective surgery and found that intraoperative monitoring with BIS was associated with a lower incidence of delirium, "possibly by reducing extreme low BIS values."[6] In a third study, a retrospective analysis of patients undergoing general anesthesia found a trend toward less POD with BIS-guided compared to end-tidal anesthetic concentration guided protocols.[16]

Near-infrared spectroscopy (NIRS) can be used to monitor the balance between cerebral oxygen delivery and consumption.[17] There is moderate to close correlation between regional cerebral oxygen saturation ($rScO_2$) and mixed venous saturation (SvO_2) in awake and anesthetized patients, indicating that $rScO_2$ is reflective of not only cerebral, but also systemic oxygen balance.[18,19] A longitudinal study of healthy elderly patients undergoing abdominal surgery found that intraoperative cerebral desaturations occurred in 25% of patients and was associated with a higher incidence of early postoperative cognitive decline and longer hospital stays.[20] Murkin et al.[7] randomized 200 patients undergoing coronary artery bypass to either NIRS monitoring with active treatment of cerebral desaturations or usual care and found that active treatment significantly decreased mortality and major organ morbidity (stroke, myocardial infarction, ventilation > 48 hours). There are no studies evaluating outcomes with the use of NIRS monitoring with a predetermined treatment protocol on outcomes after noncardiac surgery.

There is conflicting literature as to the relationship between intraoperative hypotension and POD.[21,22] A recent abstract found that nearly half of elderly patients had intraoperative mean arterial BP (MAP) decreases of 20% or more from baseline.[22] While these investigators did not find a relationship between intraoperative hypotension and POD, their findings suggest that intraoperative blood pressure variance may have an impact on the occurrence of POD.

4. Study Procedures

a. Study Design: prospective, randomized, clinical trial with a parallel arm including patients who sign the consent to be enrolled in the study but are not randomized because they have a Mini-Mental State examination score < 15.

b. Patient Population: This study will include 160 adults, aged ≥ 65 years, scheduled for surgery to repair a hip fracture at the University of Missouri-Columbia hospital. We plan to recruit 250 subjects to allow for 90 subjects to be excluded if their surgery is moved to another site or they fail the MMSE prior to completion of the study. The subjects will be recruited for the study after they are admitted to the University hospital for care of their hip fracture. They will be visited during the hospitalization. After discharge from the hospital, they will be called at home

at 1 year after surgery and this will be the final subject contact during the study. They will not be required to return to the hospital for the purposes of this study.

c. Intraoperative care – All patients will be monitored with standard ASA monitors and normocarbia and normothermia will be maintained during surgery. None of the patients will be given benzodiazepine premedication. All patients will receive a fascia iliaca compartment block in the holding area prior to surgery unless contraindicated (patient refusal, anticoagulation). Patients will be randomized to one of two intraoperative anesthesia care groups. The patients, surgeons, and research personnel performing the confusion assessments will be blinded to the study group. The anesthesia providers will be aware of the study group. For the remainder of their intraoperative anesthesia care, patients will be **randomized** to:

1. Usual care – General anesthesia will be induced with the medications commonly used for general anesthesia for this type of surgery namely, iv propofol or etomidate, iv fentanyl, and iv neuromuscular blocking agents to facilitate endotracheal intubation. Patients will be ventilated with air/oxygen mixtures during surgery and anesthesia will be maintained with sevoflurane. Anesthetic administration will be titrated on the basis of clinical judgment. A BIS® (Covidien) monitor and Fore-Sight® cerebral oximeter (CASMED) will be placed on the patients in the usual care arm, but the anesthesia team will be blinded to this monitoring data. This data will not be used to treat the patient, but it will be analyzed to determine differences in intraoperative hemodynamics, cerebral oxygenation, and depth of anesthesia between groups.

2. Optimized general anesthesia care (OP Care) – The anesthesia providers will be trained on the OP care protocol prior to the start of the study. The same anesthetic agents will be used for induction and maintenance as in the usual care group, but the maintenance anesthesia will be titrated to achieve a BIS value between 40 and 60. Non-invasive cerebral oximetry (Fore-Sight) will be placed before the induction of anesthesia and resting baseline $rScO_2$ and BIS levels will be obtained on room air prior to sedation. Intraoperative interventions will be performed for:

a. Cerebral desaturations - defined as an $rScO_2 < 50\%$ or a 15% bilateral or unilateral reduction from baseline values. If a desaturation occurs, patients will be treated using an algorithm developed by Denault et al.[23] This algorithm brings BP to baseline values, increases oxygen delivery, and corrects head position, hypoventilation, and anemia.

b. BP aberrations – any intraoperative systolic BP change greater than 20% from preoperative values and/or systolic BP < 90 mm Hg will be treated. The initial treatment of hypotension will include fluid bolus followed by vasoactive agents (phenylephrine, ephedrine, glycopyrrolate) if needed. Vasoactive drugs (hydralazine, beta blockers) will be used to treat hypertension. The anesthesiologist will use clinical judgment to determine the treatment regimen.

IV. Perioperative assessments

1. Hip Fracture Management Protocol – all patients will be managed by the Hip Fracture Improvement Team according to the hip fracture management protocol. Postoperative pain management is outlined in this protocol.

2. Cognitive and functional assessments – at baseline prior to surgery (This is a research procedure)

    a. Mini-Mental State Examination (MMSE-2)[24] - a widely used screening tool for assessing global cognition (maximum score is 30); Controlled Oral Word Association (COWA)[25] –a brief measure of lexical fluency in which the subject must generate words beginning with specific letters; and Trails Making Test[25] –a cognitive flexibility task.

    b. Depression will be measured using the Geriatric Depression – Short Form.[26]

    c. Pre-injury functional status will be evaluated using 7 instrumental and 7 basic activities of daily living (ADL).[27]

    d. Fragility Risk Analysis Index (RAI)[28] - The RAI is a novel frailty index for use in surgical populations. It is a 14-item questionnaire that takes less than 2 minutes to complete and generates scores ranging from 0 to 81.

e. Grip strength measured by the JAMAR handgrip dynamometer[29] – an instrument for measuring the maximal isometric strength of the hand and forearm muscles. The subjects are verbally encouraged to produce their maximal grip strength for 2-4 seconds for a total of 3 trials. This measurement can be completed in one minute or less. The maximal value will be used for analysis.Pain assessments –

3. Patients will be asked to verbally rate their pain at each delirium assessment using a numerical rating scale from 0 (no pain) to 10 (worst imaginable pain). (This is a research procedure). Patients will also be assessed using the Critical-Care Pain Observation Tool (CPOT). This assessment can be used in intubated or delirious patients who cannot verbally rate their pain and will be performed by the member of the research team during the research visits.

4. Delirium assessments - During the preoperative interview, the presence of delirium will be measured using the Confusion Assessment Method (CAM) and observation (appendix). The CAM [30] uses 4 clinical criteria to diagnose delirium: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. The CAM was developed to be administered by nonpsychiatric clinicians and, across studies, has a pooled sensitivity of 86% and specificity of 93%, a positive and negative predictive accuracy of greater than 90%, and high inter-rater reliability (kappa = .81 to 1.0.[28] If the subject has a positive CAM at preoperative testing, he/she will be excluded from the study. For the first five postoperative days, subjects will be visited daily by a trained research technician. The patients will be assessed daily using the CAM, the CAM-ICU and the 3D-CAM. If the CAM is positive, the diagnosis of delirium will be confirmed by a second investigator who has specialty training in evaluating delirium and is unaware of the treatment assignment for the subject and the baseline cognitive test scores. The specialist will administer the Delirium Rating Scale-Revised-98 (DSR-R98) daily until the delirium resolves or the patient is discharged.[34] The severity and duration of delirium will be recorded. (This is a research procedure.)

5. Systemic Inflammatory Response (SIRS) markers:

   The subjects will undergo venipuncture on the morning of surgery (prior to the start of anesthesia) and a total of 6 ml blood will be collected (for whole blood, serum, plasma). Blood will also be drawn at the end of surgery and on postoperative day 2 so a total of 18 ml of blood will be collected for study purposes. All blood will be treated as follows: whole blood will be stimulated *ex vivo* with LPS for 24 hours at 37 °C, as described by Riyaz with 10 ng/ml (final concentration) *Escherichia coli* lipopolysaccharide (Difco, Detroit, MI). Serum and plasma samples will be spun at 3000 rpm for 15 minutes and the supernatant stored at -80 °C until analyses are performed. After 24 hours, the TruCulture incubation will be terminated, as described and samples stored until analyses. The resulting plasma samples (+/- LPS) will be used for cytokine analyses. These blood samples will be stored until funding is obtained for analysis of the inflammatory response. (This is a research procedure to obtain pilot data on the relationship between preoperative inflammatory state and POD.

6. Postoperative follow up: patients will be contacted at 3 months and 1 year after surgery to determine postoperative complications, functional status, and living environment (independent versus assisted living or nursing home).

5. Inclusion/Exclusion Criteria

Inclusion Criteria: a. Subject or legal representative has voluntarily signed the informed consent approved by the IRB, b. hip fracture surgery scheduled under general anesthesia, c. subject is 65 years or older on the day of surgery

Exclusion Criteria: a. Inability to follow directions or comprehend the English language, b. Severe uncorrected visual or auditory handicaps, c. delirium at screening or baseline, , d. emergency surgery in which the preoperative care of the patient is not optimized by the hip fracture or primary care team.

Parallel arm 1: During the initial hospital visit, we ask the patient to state his/her name and the year. If they can correctly answer these questions, we explain the protocol and attempt to obtain

informed consent. If the patient is unable to answer these two questions, we do not attempt to enroll the patient because he/she would not be able to follow directions to take the preoperative cognitive tests. The nurses caring for these patients do CAM screening several times each day to assess the patient for delirium. After the patient is discharged from the hospital, we will perform a retrospective chart review to determine the incidence of postoperative delirium (as assessed by the nursing staff) in this patient population.

Parallel arm 2: If a patient is enrolled in the study, but scores < 15 on the MMSE, they will remain in the study but will not be randomized to one of the treatment groups. They will be given the depression (GDS) and activities of daily living (ADL) questionnaires, but will not be administered the COWA or the Trail-making tests. However, they will receive the same type of general anesthesia for their hip fracture surgery and will be assessed for pain and delirium after surgery as described in 3 and 4 above. They will not be monitored with BIS or cerebral oximetry during the surgical procedure.

6. Drugs/ Substances/ Devices

a. Drug selection: We are using the anesthetic agents routinely used during anesthesia care for hip fracture in both study groups. The anesthetic management is routine care. The only difference is that in the optimized anesthesia care group, the amount of intraoperative anesthetic given will be titrated using a depth of anesthesia (BIS) monitor. All of the drugs used in this protocol are being administered in approved dosages for FDA approved indications. The use of the BIS and Fore-Sight monitors are for the purposes of the research.

b. Device selection: We are using the depth of anesthesia device (BIS) that is already available in the University Hospital operating rooms. However, most clinicians prefer to follow clinical signs such as BP and heart rate to adjust the anesthetic depth and the anesthesia providers at the University Hospital do not routinely use the BIS for this purpose. The BIS is a FDA approved monitor intended depth of anesthesia monitoring, but it is not a standard of care. The cerebral oxygenation monitor (Fore-Sight) is often used to monitor oxygenation of the brain during

cardiac surgery. It is a FDA approved monitor and has an indication linking its' use to improved patients outcomes after surgery.

7. Study Statistics

Outcome Variables:

To assess the **primary hypothesis**, the DRS-R98, a 16-item clinician-rated scale with 13 severity items and 3 diagnostic items (maximum total score of 46 and a maximum severity score of 39 points) will be utilized.[31] The DRS-R98 is widely utilized in clinical and research situations when a sensitive, valid standardized measurement of delirium is needed. For the **secondary hypotheses**, we will collect data on the incidence of POD which will be a dichotomous outcome. The duration of delirium episodes and length of stay in the hospital will be measured in days and analyzed as a continuous variable.

Statistical Analysis: Group comparisons on the delirium severity score and length of stay will be made using the Wilcoxon Rank Sum Test (WRST). The WRST is a nonparametric alternative to the two sample t-test. The standard assumptions of the t-test are normality and equal variances, neither of which is required for the WRST. Hospital length of stay (LOS) is typically a highly skewed outcome due to a relatively few patients having atypically long LOS. Thus the WRST will also be used for a simple two-group comparison and results reported in terms of median LOS. Log-transformed LOS will be the dependent variable if regression analysis is needed for covariate adjustment.

Randomization only *guarantees* homogeneous groups when randomizing a very large number of subjects. Thus, preliminary comparison of the baseline characteristics of the usual care and study group will be performed to confirm that randomization did indeed produce similar groups with respect to demographics and initial cognitive status. Any statistically significant ($p < 0.05$) differences that are also judged to be clinically meaningful will shift the analytical approach to an analysis of covariance using either parametric or non-parametric regression methods most appropriate to the specific outcome.

We will also collect data on intraoperative variables including the average BIS and BP as well as the proportion of time that the BP and BIS is in the recommended range. This information will be analyzed as a quality control measure to ensure compliance with the treatment protocol in the optimal care group.

Data for the treatment group (OP Care) will be analyzed after the first 5 patients and then after each additional 15 patients are treated to ensure compliance with the treatment protocol (BP and BIS in recommended range). Patients will be followed daily during the hospitalization and charts reviewed to determine transfusion requirements and prevalence and types of postoperative complications.

Power Analysis: The primary hypothesis states that optimized anesthesia care will decrease the severity of POD compared to usual care. We expect that the severity score in the optimized group will be 14 ± 3 versus 18 ± 4 in the usual care group similar to that seen in previous treatment studies.[35] To have 80% power to detect such a difference when testing a two sided alternative and alpha of 0.05 will require 22 subjects per group. This is the number of subjects that qualify as confused. Only patients with POD contribute to the DRS severity sample, so if 30% of subjects are expected to experience delirium, then the total sample size for the study would have to be 44/.3 = 148, or 74 per group. We plan to enroll 80 patients per group for a total sample size of 160.

Interim Analysis: There will be no interim analyses and no safety monitoring board so there are no early stopping rules.

Data management

The data collected on the data collection forms developed for this study, will be obtained specifically for research purposes. Research data will be stored in a locked research office in the Department of Anesthesiology at the University Hospital. All patient identifiable information will be stored in a locked file cabinet in this locked research office or stored on a secure server in this locked office. Only research personnel listed on the IRB proposal will know the log in and password information for this server. The demographic, hemodynamic, laboratory and historical data that are collected at the time of the intraoperative study are part of the routine medical record documenting the patient's care in the perioperative period. The patient's identity will be specifically protected and confidentiality will be maintained in any publication of data.

8. Risks

This study will enroll 160 patients scheduled for surgery for repair of a hip fracture. All subjects will have an injury requiring surgery and general anesthesia is routinely used at the University of Missouri-Columbia for repair of a hip fracture. The anesthesia used in the protocol is routine care and does not add additional risk to the patients. In the optimized care group, we will apply two additional monitors, a cerebral oximeter and a depth of anesthesia monitor. Both of these monitors are non-invasive and FDA approved for use in the operating room so the additional risk of using these monitors is minimal. Both devices use a bandage-like sensor applied to the forehead. There are no reports of allergies or rashes from these sensors.

The Hip Fracture Improvement Team evaluates all patients who are admitted to the University Hospital with this type of injury and they will evaluate all of the patients in the study and adhere to the Hip Fracture Management Protocol in the perioperative period. Thus, the perioperative care of the patient will be unchanged for patients enrolled in this study.

Elderly patients with hip fractures may have cognitive impairment and ensuring informed consent can be a challenge in this type of patients. Patients will not be enrolled in the study if they are delirious when approached and will be excluded from the study if they exhibit significant cognitive impairment as evidenced by a score < 18 on the baseline MMSE. However, inclusion of older adults with cognitive impairment in research studies in necessary because preoperative cognitive impairment is one of the primary risk factors for POD.[32,31] We will request IRB approval to obtain consent from a legally authorized representative (as outlined in a Missouri statute) if a subject's decision-making capacities are in question. If the subject agrees to the research protocol, but we are unsure of his/her ability to fully understand the research, we will obtain additional informed consent from a family member or legal representative.

The baseline cognitive and functional tests and questionnaires are brief and are not adverse. These tests, however, can be frustrating for older subjects. To prevent this problem, the test battery is limited to approximately 15 min and we will ask the subject if he/she needs a break during testing. We will also have

water, soda and snacks available for the subjects during testing. If a subject wants to stop the testing at any time, we will not continue testing him/her.

There are always risks associated with the breach of a subject's confidentiality. To minimize this risk, research data will be stored in a locked research office in the Department of Anesthesiology at the University Hospital. All patient identifiable information will be stored in a locked file cabinet in this locked research office or stored on a secure server in this locked office. Only research personnel listed on the IRB proposal will know the log in and password information for this server. The demographic, hemodynamic, laboratory and historical data that are collected at the time of the intraoperative study are part of the routine medical record documenting the patient's care in the perioperative period. The patient's identity will be specifically protected and confidentiality will be maintained in any publication of data.

9. Benefits

In general, the research procedures will not benefit the individual participant. Subjects in both groups will be monitored closely and will receive the type of general anesthesia that would be used if they were not enrolled in the study. It is possible that patients in the optimized anesthesia care group will have better outcomes, but this is not known. The primary benefit of this project is to society as a whole, from the new information that will be obtained regarding the role of optimized anesthesia care in preventing POD and improving postoperative outcomes.

10. Payment and Remuneration

There will be no compensation or payments to participants in this study.

11. Costs

The subjects in the study will not be responsible for any of the additional costs associated with the research procedures. The additional costs in the study include the costs of the sensors for the BIS and Fore-Sight monitors. These sensors will be paid for by research funds in the Department of Anesthesiology at the University of Missouri. Funding will be sought for analysis of the blood samples for the inflammatory response. The blood samples will be stored until this funding is obtained.

12. References

1. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM: Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc 2001; 49: 516-22

2. Lundstrom M, Olofsson B, Stenvall M, Karlsson S, Nyberg L, Englund U, Borssen B, Svensson O, Gustafson Y: Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study. Aging Clin Exp Res 2007; 19: 178-86

3. Sieber FE, Zakriya KJ, Gottschalk A, Blute MR, Lee HB, Rosenberg PB, Mears SC: Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. Mayo Clin Proc 2010; 85: 18-26

4. Palmbergen WA, van Sonderen A, Keyhan-Falsafi AM, Keunen RW, Wolterbeek R: Improved perioperative neurological monitoring of coronary artery bypass graft patients reduces the incidence of postoperative delirium: the Haga Brain Care Strategy. Interact Cardiovasc Thorac Surg 2012; 15: 671-7

5. Chan MT, Cheng BC, Lee TM, Gin T, Group CT: BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013; 25: 33-42

6. Radtke FM, Franck M, Lendner J, Kruger S, Wernecke KD, Spies CD: Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 2013; 110 Suppl 1: i98-105

7. Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, Cleland A, Schaefer B, Irwin B, Fox S: Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study. Anesth Analg 2007; 104: 51-8

8. Rudolph JL, Marcantonio ER: Review articles: postoperative delirium: acute change with long-term implications. Anesth Analg 2011; 112: 1202-11

9. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK: One-year health care costs associated with delirium in the elderly population. Arch Intern Med 2008; 168: 27-32

10. Franco K, Litaker D, Locala J, Bronson D: The cost of delirium in the surgical patient. Psychosomatics 2001; 42: 68-73

11. Inouye SK, Charpentier PA: Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA 1996; 275: 852-7

12. Shim JJ, Leung JM: An update on delirium in the postoperative setting: prevention, diagnosis and management. Best Pract Res Clin Anaesthesiol 2012; 26: 327-43

13. Bjorkelund KB, Hommel A, Thorngren KG, Gustafson L, Larsson S, Lundberg D: Reducing delirium in elderly patients with hip fracture: a multi-factorial intervention study. Acta Anaesthesiol Scand 2010; 54: 678-88

14. Zhang H, Lu Y, Liu M, Zou Z, Wang L, Xu FY, Shi XY: Strategies for prevention of postoperative delirium: a systematic review and meta-analysis of randomized trials. Crit Care 2013; 17: R47

15. Neuman MD RP, Ludwig JM, Zubizarreta JR, Silber JH: Anesthesia technique, mortality and length of stay after hip fracture surgery. JAMA 2014; 311: 2508-2517

16. Whitlock EL, Torres BA, Lin N, Helsten DL, Nadelson MR, Mashour GA, Avidan MS: Postoperative delirium in a substudy of cardiothoracic surgical patients in the BAG-RECALL clinical trial. Anesth Analg 2014; 118: 809-17

17. Murkin JM: Cerebral oximetry: monitoring the brain as the index organ. Anesthesiology 2011; 114: 12-3

18. Paarmann H, Heringlake M, Heinze H, Hanke T, Sier H, Karsten J, Schon J: Non-invasive cerebral oxygenation reflects mixed venous oxygen saturation during the varying haemodynamic conditions in patients undergoing transapical transcatheter aortic valve implantation. Interact Cardiovasc Thorac Surg 2012; 14: 268-72

19. Schoen J, Meyerrose J, Paarmann H, Heringlake M, Hueppe M, Berger KU: Preoperative regional cerebral oxygen saturation is a predictor of postoperative delirium in on-pump cardiac surgery patients: a prospective observational trial. Crit Care 2011; 15: R218

20. Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Montanini S, Collaborative Italian Study Group on Anaesthesia in Elderly P, Danelli G, Nuzzi M, Mentegazzi F, Torri G, Martani C, Spreafico E, Fierro G, Pugliese F, De Cosmo G, Aceto P, Servillo G, Monaco F: Monitoring cerebral oxygen saturation in elderly patients undergoing general abdominal surgery: a prospective cohort study. Eur J Anaesthesiol 2007; 24: 59-65

21. Williams-Russo P, Sharrock NE, Mattis S, Liguori GA, Mancuso C, Peterson MG, Hollenberg J, Ranawat C, Salvati E, Sculco T: Randomized trial of hypotensive epidural anesthesia in older adults. Anesthesiology 1999; 91: 926-35

22. Hirsch J DG, Tsai TL, Sands LP, Leung JM: Intraoperative blood pressure variance, not hypotension impacts early postoperative delirium. Anesthesiology 2013: A3015

23. Denault A, Deschamps A, Murkin JM: A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy. Semin Cardiothorac Vasc Anesth 2007; 11: 274-81

24. 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; 12: 189-98

25. Spreen O SE: A compendium of neuropsychological tests, 2nd edition. New York, Oxford, Oxford University Press, 1998

26. Bass DS, Attix DK, Phillips-Bute B, Monk TG: An efficient screening tool for preoperative depression: the Geriatric Depression Scale-Short Form. Anesth Analg 2008; 106: 805-9, table of contents

27. George LK, Fillenbaum GG: OARS methodology. A decade of experience in geriatric assessment. J Am Geriatr Soc 1985; 33: 607-15

28. Melin AA, Schmid KK, Lynch TG, et al. Preoperative frailty Risk Analysis Index to stratify patients undergoing carotid endarterectomy. *Journal of vascular surgery.* 2015;61:683-89.

29. Hamilton GF, McDonald C, Chenier TC. Measurement of grip strength: validity and reliability of the sphygmomanometer and JAMAR grip dynamometer. JOSPT 1992; 16: 215-19

30. 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; 113: 941-8

31 Trzepacz PT, Mittal D, Torres R, Kanary K, Norton J, Jimerson N: Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci 2001; 13: 229-42

32. Greene NH, Attix DK, Weldon BC, Smith PJ, McDonagh DL, Monk TG: Measures of executive function and depression identify patients at risk for postoperative delirium. Anesthesiology 2009; 110: 788-95

33. Smith PJ, Attix DK, Weldon BC, Greene NH, Monk TG: Executive function and depression as independent risk factors for postoperative delirium. Anesthesiology 2009; 110: 781-7