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Original contribution

The effect of desflurane versus propofol anesthesia on postoperative delirium in elderly obese patients undergoing total knee replacement: A randomized, controlled, double-blinded clinical trial☆

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ABSTRACT

Study objective: The goal of this study was to investigate the incidence of delirium, wake-up times and early post-operative cognitive decline in one hundred obese elderly patients undergoing total knee arthroplasty.
Design: Prospective randomized trial.
Settings: Operating room, postoperative recovery area, hospital wards.
Patients: 100 obese patients (ASA II and III) undergoing primary total knee replacement under general anesthesia with a femoral nerve block catheter.
Intervention: Patients were prospectively randomized to maintenance anesthesia with either propofol or desflurane.
Measurements: The primary endpoint assessed by a blinded investigator was delirium as measured by the Confusion Assessment Method. Secondary endpoints were wake-up times and a battery of six different tests of cognitive function.
Main results: Four of the 100 patients that gave informed consent withdrew from the study. Of the remaining 96 patients, 6 patients did not complete full CAM testing. Preoperative pain scores, durations of surgery and anesthesia, and amount of intraoperative fentanyl were not different between groups. One patient in the propofol group developed delirium compared to zero in desflurane. One patient in desflurane group developed a confused state not characterized as delirium. Fifty percent of the patients exhibited a 20% decrease in the results of at least one cognitive test on the first 2 days after surgery, with no difference between groups. There were no differences in the time to emergence from anesthesia, incidence of postoperative nausea and vomiting, and length of postanesthesia care unit (PACU) stay between the two groups.
Conclusions: In conclusion we found a low incidence of delirium but significant cognitive decline in the first 48 h after surgery. In this relatively small sample size of a hundred patients there was no difference in the incidence of postoperative delirium, early cognitive outcomes, or wake up times between the desflurane or propofol group.

1. Introduction

Elderly individuals over age 65 comprise the fastest growing subset of the American population [1], and account for an increasing number of surgeries. For example, primary total knee arthroplasty (TKA) cases are projected to grow 7 fold, by the year 2030 to 3.48 million procedures [2]. Elderly patients are at increased risk for postoperative delirium, which according to some studies occurs in 10%–60% of surgical patients [3,4]. In recent meta-analyses 17% of patients who underwent total joint replacement developed delirium during hospital admission. Individual estimates varied from 0% to 82%, but this variability was not adequately explained by the variables that were examined [5]. Increasing age is also an important risk factor for cognitive decline and prolonged recovery time from anesthesia [6,7].

While previous work has compared volatile agents [8,9], the potential different impact on cognitive outcomes including delirium between propofol and volatile agents has not been fully characterized. The use of volatile agents for maintenance, as opposed to propofol, may lower the risk of post-operative delirium and ensure a more rapid post-operative

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recovery given the more complex and variable pharmacokinetics associated with propofol. For example, geriatric outpatients undergoing brief urologic procedures may more rapidly achieve fast-tracking discharge criteria after desflurane anesthesia compared to propofol [10]. However, another study found no difference in the rate of cognitive recovery in middle-aged ambulatory breast surgery patients receiving desflurane or propofol anesthesia [11].

Recent trials have compared different general anesthetics with conflicting results. For example, a small study reported a lower incidence of postoperative delirium in elderly patients receiving propofol anesthesia when compared to sevoflurane anesthesia [12]. A more recent study showed that cognitive dysfunction in elderly patients after major surgery was higher in those receiving sevoflurane general anesthesia than those receiving total intravenous anesthesia with propofol [13]. In contrast, other studies suggest that inhalational anesthesia may be associated with less postoperative cognitive dysfunction and postoperative delirium than propofol total intravenous anesthesia [14–16].

The goal of this study was to assess the incidence of delirium, wake-up times and post-operative cognitive decline in the 48 h after surgery in one hundred obese elderly patients undergoing total knee arthroplasty with either propofol or desflurane maintenance anesthesia.

We chose TKA because it is a common surgical procedure in the elderly and we focused on obese patients because the incidence of obesity is increasing among elderly patients and while obesity is not a known risk factor for cognitive decline per se, it is as an independent major risk factor for dementia that is associated with cognitive decline [17,18].

2. Methods

2.1. Study sample

This prospective, single-center, double-blind study was approved by the Institutional Review Board of Stanford University (reg. no. H-C-FSP-2010-050). Written informed consent for participation was obtained from all patients. This study was registered at clinicaltrials.gov (NCT01270620). Incidence of delirium and wake-up times were primary endpoints. Measures of cognitive function were designated as secondary endpoints as it is unclear how much of the cognitive dysfunction in surgical patients is due to anesthesia, surgery and perioperative care without a non-surgical control group and a longer term follow-up [19]. Eligible patients consisted of those over age 65 undergoing elective TKA at a large quaternary referral academic health center (Stanford University) between October 2010 and August 2014. The study was reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) [20].

Additional inclusion criteria included an ASA physical health Class of II or III, and a body mass index (BMI) > 30 kg/m^2. Exclusion criteria were patient refusal of or failure of regional block; pre-existing neurocognitive disorders [Mini-Mental State Examination (MMSE) score ≤ 23]; and known intolerance to any of the drugs used in the study.

2.2. Study design

Study patients were randomized and enrolled, by research coordinator, on the day of surgery via computer generated random number into either the propofol or desflurane arms. Both groups received a femoral nerve block with an initial bolus of 30 ml 0.25% ropivacaine as well as placement of an indwelling catheter. Sedation with fentanyl and midazolam was provided for the femoral nerve block at the discretion of the regional anesthesia team. For induction, both groups received propofol (1 mg/kg), followed by fentanyl (1–2 mcg/kg), and rocuronium (0.4 mg/kg), all dosed according to lean body weight.

After induction, anesthesia was maintained with propofol or desflurane, based on the treatment arm to which the patient was assigned. In addition to standard monitors, a Sedline ® monitoring sensor was used to monitor the depth of anesthesia using the Patient State Index (PSI, Masimo, Irvine, USA). The maintenance agent was titrated to a PSI of 30–50 using the algorithm described in the supplemental content. No prophylactic anti-emetics drugs were given during surgery. Following the surgery, a continuous infusion of 0.2% ropivacaine at 6 ml/h was initiated in the recovery room and adjusted to a maximum of 10 ml/h for the next 48 h. In addition, all patients were provided with a patient-controlled analgesia (PCA) device programmed to administer intravenous hydromorphone with a standardized dosing and lock-out period. While the anesthesiologist could not be blinded because of the different administration techniques for the two anesthetics, the surgeons, study investigators, and patients were blinded to randomization, so our design produced a double-blind study. Further details of our study design can be found in the online supplemental content.

2.3. Outcomes

The incidence of postoperative delirium was measured by the confusion assessment method (CAM), a commonly used instrument for measuring postoperative delirium [21,22]. In brief, CAM is a screening instrument that assesses four criteria: (1) acute onset/fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. Delirium is considered present when both of the first two criteria and either the third or fourth criteria are present. We administered the instrument at baseline, 1, 6, 24 and 48 h after surgery. Delirium was considered present when the CAM criteria were satisfied at any of the postoperative assessment points or during the immediate period previous to assessment documented in the chart. To ensure consistency, the same research assistant trained in the use of the CAM evaluated all patients, performed a chart review and check with nurses about patient mental status covering time spam between assessments. Nurses in the orthopedic floor have been trained and were using CAM as daily basis assessment before this study started.

Cognitive function was assessed using the Digit Symbol Substitution Test (DDST) [23], the Mini Mental Status Exam (MMSE) [24], the Trail Making Test, the Digit Span subtest (DST) [25] of the Wechsler Adult Intelligence Scale (Revised), and the Geriatric Depression Scale (GDS) [26]. In brief, the DSST is a measure of attention, working memory, sustained visual attention, and psychomotor speed, while the MMSE is a brief screening test for detecting chronic cognitive impairment. The DST is a test of attention and working memory, the TMT is a test of executive function, and the GDS is a screen for depression. Each of these measures has been previously used to assess cognitive function. Further description of these tests can be found in the supplemental content. We defined a 20% decrease from baseline in any of the tests as indicative of cognitive decline [27].

In addition, we also examined the effect of maintenance agent on wake-up times, length of PACU stay, pain scores and the incidence of post-operative nausea/vomiting. Wake-up times were measured as the amount of time between discontinuation of the given maintenance agent and (1) spontaneous breathing, (2) eye opening, (3) tracheal extubation, and (4) ability to follow commands. A research assistant present in the operating room captured those measurements. Length of PACU stay was measured as the amount of time between PACU admission and discharge based on medical record data using fast-track tool [28]. Postoperative nausea/vomiting was measured as being present or not. Pain scores were evaluated by verbal numeric pain scale where 0 reflected no pain and 10 reflected worst possible pain. Both of these measures were evaluated at 1 h and at 6–8 h following the end of surgery.

2.4. Statistical analyses

Previous work has found a wide variety of estimates on the incidence of our primary outcome, post-operative delirium. One study found an incidence of 26% among patients undergoing orthopedic surgery [29], while another meta-analysis found estimates ranging from 3 to 28% among patients undergoing elective orthopedic surgery [30].