Supplemental sedation with propofol or light general anesthesia with desflurane as adjuncts to general anesthesia in patients undergoing total hip replacement: a randomized pilot study assessing the effect on cognitive recovery

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ABSTRACT
Background: Total hip replacement is a common procedure, but despite low incidences of mortality and major complications, these patients remain susceptible to postoperative cognitive decline. Our aim was to determine the impact of supplemental sedation and light general anesthesia to supplement spinal anesthesia, on cognitive recovery using “The Postoperative Quality of Recovery Scale”.
1.0. INTRODUCTION

Total hip replacement is a frequently performed surgical procedure, and despite the procedure’s substantial invasiveness, advances in preoperative medical optimization and evidence-based clinical care have led to low incidences of mortality and major complications. Nevertheless, patients undergoing major joint arthroplasty remain susceptible to postoperative cognitive decline (POCD), with rates reported as high as 75%, depending on the definition, patient population, and assessment tool. Importantly, POCD can lead to delayed mobilization, prolonged hospital admission, and increased mortality and morbidity. Therefore, POCD has substantial impact on health resource utilization and may be associated with significant economic costs and reduced health-related quality-of-life.

Indeed, the etiology of POCD is multifactorial and includes several unmodifiable factors such as age and pre-existing cognitive impairment. However, there are also numerable modifiable factors such as perioperative pain management, and type of anesthetic technique. Total hip replacement surgery is commonly performed under spinal anesthesia with either supplemental sedation or light general anesthesia. However, no consensus exists concerning anesthetic technique in these patients and there are proponents citing advantages to either technique. For instance, anesthetists advocating general anesthesia may argue that prolongation of the surgical procedure induces a risk of ‘over sedation’ leading to hypoventilation, and hypercarbia, with potential complications such as POCD and/or delirium.

In this pilot study, the aim was to assess the impact of supplemental sedation with intravenous propofol and light general anesthesia with desflurane general anesthesia. In both groups, cognitive recovery rates improved over time to 85% with propofol group and 100% with desflurane group after 3 months, with no apparent difference 3 days after surgery. Similarly, overall recovery rates improved to 79% in the propofol group and 83% in the desflurane group after 3 months. In the four remaining subdomains 3-month recovery rates in the propofol and the desflurane groups were: nociception; 97% and 100%, respectively, emotion; 90% and 90%, respectively, and activity-of-daily-living; 93% and 95%, respectively.

Conclusion: The use of desflurane general anesthesia to supplement spinal anesthesia for total hip replacement surgery might have a modest benefit for late but not early cognitive recovery compared to intravenous sedation with propofol.

Key words: Postoperative quality of recovery; Postoperative Quality of Recovery Scale; Postoperative cognitive decline; Total hip replacement; Spinal anesthesia; Treatment outcome
to determine the effects of the two strategies on overall quality recovery as well as the other recovery domains (physiological, nociceptive, emotional, and activity-of-daily-living recovery) up to 3 months after surgery.

2.0. METHODS

The local institutional ethical review board from the Epworth Hospital Human Research Ethics Committee approved the study, which conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study is listed on anzctr.org.au (ACTRN1261300805774) and written informed consent was obtained from all patients. The initial study was terminated early as a pilot study due to multiple competing randomized trials at the institution limiting potential recruitment. Randomization of patients was performed using a computer-generated randomization sequence, without blocking, and the allocation information for each patient was given to the treating anesthetist in a double, opaque, sealed envelope. Allocation information was concealed for all study personnel until completion of the study. This manuscript adheres to the applicable Consort guidelines.

2.1. Design and study participants

In a prospective, randomized pilot study, patients were recruited from Epworth HealthCare, Richmond, Australia. Inclusion criteria were age of 18 years or above and undergoing total hip replacement surgery under spinal anesthesia. Exclusion criteria were non-fluent English language in order to ensure that patients were able to answer the quality-of-recovery questionnaire adequately.

As an adjunct to spinal anesthesia, patients were randomized to either propofol sedation or desflurane general anesthesia. None of the patients received any premedication other than analgesic such as paracetamol. Following establishment of intravenous access and appropriate monitoring, spinal anesthesia was administered with 3.0-3.5 ml of plain 0.5% bupivacaine combined with preservative free morphine 50-150 mcg or fentanyl 7.5-15 mcg. After confirmation of correctly working spinal anesthesia, the patient received either propofol sedation by continuous intravenous infusion or desflurane anesthesia depending on the randomization. Postoperatively, analgesia consisted of oral or systemic opiates in addition to regular multimodal oral analgesia including paracetamol and non-steroidal anti-inflammatory drugs.

2.2. Intervention

Patients, receiving propofol infusion, had a dose adjusted according to sedation requirements by the anesthetist. Patients were spontaneously ventilating with supplemental oxygen administered via a clear Hudson mask at 6 to 8 liters/minute.

Patients receiving desflurane anesthesia received intravenous induction of anesthesia with propofol, and the dose of desflurane was adjusted according to the clinical requirements by the anesthetist. Patients were spontaneously ventilating via laryngeal mask unless the treating anesthetist considered endotracheal intubation and mechanical ventilation required.

2.3. Data collection

Recovery after surgery was assessed using the “Postoperative Quality of Recovery Scale” (PostopQRS) of which details of the construct and validation has been previously published12-15 (see www.postopqrs.com). In brief, quality of recovery is measured using a verbal survey tool that measures recovery in five subdomains; physiological, emotive, nociceptive, functional (activity-of-daily-living), and cognitive recovery. The tool is designed for repeated measurements and can be administered either face-to-face or via the telephone.13

Prior to surgery, baseline measurements are acquired, and recovery is a dichotomized
outcome defined as a return to baseline values or better at each of the postoperative time points in each of the five domains. Overall recovery requires recovery in all subdomains being assessed. The cognitive subdomain consists of five verbal tests, and the subdomain requires recovery in all five tests, which are orientation (to name, place, and date of birth), digits forward, digits back, word recall, and word generation.$^{12,13}$ Variance in cognitive performance is a normal event and accordingly the definition of recovery in cognitive tests includes a tolerance factor to account for normal variability.$^{13}$ This means that patients are allowed to perform a little worse than their baseline performance and still be scored as recovered. However, if the baseline score is less than the tolerance factor, they would automatically be scored as recovered, and accordingly, patients with ‘low baseline scores’ cannot be evaluated for cognitive recovery. Further, they are excluded from overall recovery, unless they fail recovery in another subdomain as any failed recovery subdomain results in failure of the overall recovery. The incidence of low baseline scores differs amongst populations, being near zero in young volunteers$^{13}$ and 5-15% in orthopedic patients.$^{15}$

The PostopQRS was conducted just prior to surgery (baseline), and at 15 minutes, 40 minutes, 1 day, 3 days, 1 month, and 3 months after surgery. The physiological domain was measured only at 15 minutes, 40 minutes, and 1 day. An assessment of patient perspective was performed as a part of the PostopQRS at 1 day, 3 days, 1 month, and 3 months after surgery. This included ability to work, ability to undertake daily living activities, clarity of thought, and satisfaction with the anesthetic care received.

2.4. Outcomes

The primary endpoint was the incidence of failure to cognitively recover 3 days after total hip replacement. Secondary endpoints were failure to recover in the overall domain and in the 5 subdomains (physiology, nociception, emotion, cognition, and activities of daily living - ADL) during the 3-month follow-up period.

2.5. Statistical analyses

Data are presented as means ± standard deviations or as absolute numbers with percentages of patients. No comparisons were performed for quality of recovery over time due to low patient numbers. The original study was to include 200 participants, based on ability to detect an odds ratio of 2.5 for cognitive recovery on Day 3, with a two-tailed design, alpha value of 0.05 and power of 0.8. The study was terminated as a pilot study as competing clinical trials made it unfeasible to complete the trial in a reasonable time frame. Descriptive data were stored in Microsoft Excel 2016 (Microsoft Corp., CA, USA) and for statistical analyses we used Stata/IC 12.1 for Mac (Stata Corp., TX, USA).

3.0. RESULTS

In the period from August 2014 to March 2016, 52 patients were enrolled after which the study was terminated due to low recruitment numbers. At this point 31 patients were randomized to propofol and 21 patients to desflurane as displayed in Fig. 1. All the enrolled patients had complete baseline assessments of which three patients had low baseline cognitive scores.

Baseline characteristics and operative details are shown in Table 1. As displayed, mean ages were 63.1±12.1 years in the propofol group and 62.8±13.1 years in the desflurane group. Generally, the groups were similar although there were tendencies towards fewer males and better ASA status in the propofol group.
Table 1. Characteristics and operative details of patients undergoing total hip replacement surgery

<table>
<thead>
<tr>
<th></th>
<th>Propofol n = 31</th>
<th>Desflurane n = 21</th>
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</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.1 ± 12.1</td>
<td>62.8 ± 13.1</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>8 (26)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27 ± 6</td>
<td>29 ± 7</td>
</tr>
<tr>
<td>Alcohol consumption, units/day</td>
<td>5 ± 6</td>
<td>7 ± 8</td>
</tr>
<tr>
<td>Years in full-time education, years</td>
<td>14 ± 4</td>
<td>15 ± 3</td>
</tr>
<tr>
<td>Employment, n (%)</td>
<td>14 (45)</td>
<td>13 (62)</td>
</tr>
<tr>
<td><strong>ASA status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA I</td>
<td>10 (32)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>ASA II</td>
<td>14 (45)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>ASA III</td>
<td>7 (23)</td>
<td>10 (48)</td>
</tr>
<tr>
<td>ASA IV - VI</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
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<tr>
<td>Active smokers, n (%)</td>
<td>2 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Former smokers, n (%)</td>
<td>14 (45)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Non-smokers, n (%)</td>
<td>15 (48)</td>
<td>10 (48)</td>
</tr>
<tr>
<td><strong>Perioperative data</strong></td>
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<tr>
<td>Duration of anesthesia, minutes</td>
<td>110 ± 27</td>
<td>100 ± 28</td>
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<td>Pre-operative hypnotic drug, n (%)</td>
<td>19 (61)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Intra-operative vasopressors, n (%)</td>
<td>18 (58)</td>
<td>17 (81)</td>
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<tr>
<td>Intra-operative opiates, n (%)</td>
<td>21 (68)</td>
<td>17 (81)</td>
</tr>
<tr>
<td>Post-operative opiates, n (%)</td>
<td>22 (71)</td>
<td>15 (71)</td>
</tr>
<tr>
<td>Post-operative antiemetic drug, n (%)</td>
<td>18 (58)</td>
<td>9 (43)</td>
</tr>
</tbody>
</table>

Data reported as means ± standard deviations or absolute numbers and percentages of patients. ASA, American Society of Anesthesiology Physical Classification System
Figure 1.
Flow of patients during the study period.

Quality of recovery over time is illustrated in Fig. 2. Recovery improved over the follow-up period in both groups in the overall domain as well as all subdomains. There was no significant difference in cognitive recovery for the primary endpoint at Day 3 after surgery. However, there was a trend towards improved cognitive recovery for desflurane which was maximal at 3 months (propofol 85% vs. 100% desflurane). Similar trends were noted in overall recovery to reach recovery rates of 79% in the propofol group and 83% in the desflurane group after 3 months. In each of the four remaining subdomains 3-month recovery rates in the propofol and the desflurane groups were: nociception; 97% and 100%, respectively, emotion; 90% and 90%, respectively, and activities of daily living; 93% and 95%, respectively.
Figure 2

Recovery profiles of patients undergoing total hip replacement surgery under spinal anesthesia and, as an adjunct, either propofol sedation or desflurane anesthesia. The graphs display the percentages of patients recovered in the two groups at each timepoint. A) shows the cognitive recovery profile (primary endpoint), whereas B to F) show the overall domain and the four remaining subdomains.

ADL, activity of daily living

Patient perspective in terms of ability to work, ability to undertake daily living activities, clarity of thought, and satisfaction with anesthetic care is displayed in Fig. 3. There were no differences in patient perspective between groups at any time point in any of the four items.

4.0. DISCUSSION

This prospective, randomized pilot study, shows that there could be a clinically important difference in late cognitive recovery favoring light general anesthesia maintained with desflurane over propofol sedation, as adjuncts to spinal anesthesia, in patients undergoing total hip replacement surgery. As failure to cognitively recover impacts on postoperative mobilization, length of stay, and the risk of adverse clinical events, this study calls for an adequately powered, randomized trial in order to provide evidence-based recommendations to anesthetists for patients undergoing major joint replacement.

In hip and knee replacement surgery there are few data available comparing the incidences of POCD after different sedation techniques used to supplement spinal anesthesia. Rasmussen et al.\(^{16}\) conducted the only prospective, randomized trial and found no differences in POCD at neither discharge nor a 3-month follow-up between patients receiving sedation with propofol or light general anesthesia with xenon inhalation, as adjuncts to spinal anesthesia. Nevertheless, the study was not powered for showing a difference in POCD, but merely to gain an impression of potential benefits. Indeed, the study from Rasmussen and colleagues\(^{16}\) is comparable to the current study as both demonstrate the feasibility and possible advantages of light general anesthesia compared with propofol sedation.

Other studies have compared spinal or epidural anesthesia with supplemental sedation against general anesthesia without central nerve block,\(^{17,18}\) but again, there are only limited data available on the incidence of POCD. It has been shown that general anesthesia may be associated with increased rates of POCD, but only in the early postoperative period as no differences have yet been identified beyond postoperative day 7.\(^{19-22}\) Importantly, however, later advances in the optimization of depth of anesthesia through the use of intraoperative cerebral EEG and regional oxygenation monitoring may decrease the frequency of POCD after general anesthesia, and thereby obviate the benefits of central nerve block in the early postoperative period.\(^{23}\) In all circumstances, discriminating between light general anesthesia as a supplement to spinal anesthesia and general anesthesia without nerve block, is essential as depth of anesthesia may be an important contributor to POCD.
Figure 3
Patient perspective following total hip replacement surgery under spinal anesthesia and, as an adjunct, either propofol sedation or desflurane anesthesia. **A)** shows the percentages of patients reporting “mild or no impact” on ability to work, **B)** shows the percentages of patients reporting “mild or no impact” on ability to undertake daily living activities, **C)** shows the percentages of patients reporting “no impact at all” on clarity of thought, and **D)** shows the percentages of patients reporting “satisfied or totally satisfied” with anesthetic care.
Whilst our data indicate a separation between groups in terms of cognitive recovery 3 months after surgery, which may have clinically significant implications, the pathophysiological mechanism is unclear. It has been suggested that especially older patients are frequently ‘over sedated’, and hypoventilation with hypercarbia may potentially lead to delayed cognitive recovery.\(^{10,11}\) In contrast, hypoventilation may be less likely in patients under light general anesthesia owed to maintenance of a clearer airway and pressure supported ventilation. Similarly, it remains uncertain why no group separation is noted until 1 month after surgery. However, we did not survey the patients between 3 days and 1 month, so it is unknown when group separation began. It is possible that a small, but clinically important difference, may only become apparent after the decrease in postoperative inflammation and analgesic medication requirement,\(^7\) as the medication and inflammation may mask potential differences in cognitive recovery.

It is clear that different anesthetic techniques may be appropriate in different patient populations, and in the past years there has been an increasingly widening of the indications of major joint arthroplasty to include younger as well as older populations.\(^{24-26}\) This emphasizes the importance of minimization of the risk of delayed cognitive recovery, and older patients in particular may benefit most from anesthetic techniques aimed at reducing the risk of POCD.\(^7,8,27-30\) Accordingly, large-scale randomized studies are needed not only in order to assess the potential advantages between sedation and light general anesthesia, but also to evaluate possible variances in impact on different populations.

4.1 Limitations
This study was initially powered to detect a moderate effects size on cognitive recovery at Day 3 after surgery, but was terminated early as a pilot study due to competing clinical trials affecting completion feasibility. Therefore, the study is underpowered to find a significant difference, and we urge caution in statistical interpretation due to risk of Type II error. However, the important trend identified does not relate to Day 3 after surgery, but in the longer time period (after 1 month), with a modest but clinically important difference in cognitive recovery favoring desflurane general anesthesia. This study will provide important information upon which to design a definitive randomized trial, looking for an absolute difference of 10-15%, and for more time points between 3 days and 1 month in order to capture when group separation occurs. Further, our findings cannot be extrapolated to techniques not involving spinal anesthesia without further research. There was group imbalance in allocation numbers due to the unblocked allocation sequence, though the participants were very similar, and any potential bias for ASA status favored the propofol group.

5.0. CONCLUSION
The use of desflurane general anesthesia to supplement spinal anesthesia for total hip replacement surgery might have a modest benefit for late but not early cognitive recovery compared to intravenous sedation with propofol. This pilot study should be followed by an adequately powered, randomized trial in order to provide evidence-based recommendations to anesthetists for patients undergoing major joint replacement.

6.0. DISCLOSURE OF INTEREST
The authors report no conflicts of interest.

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8.0. REFERENCES


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