Incidence of postoperative cognitive dysfunction after general or spinal anaesthesia for extracorporeal shock wave lithotripsy

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Editor’s key points
- Aspects of general anaesthesia might contribute to postoperative cognitive dysfunction (POCD).
- This study found that avoiding general anaesthesia did not reduce the risk of POCD.
- Other factors, perhaps the inflammatory response to surgery, and hospitalization, might contribute to POCD.

Background. Since general anaesthesia invariably accompanies surgery, the contribution of each to the development of postoperative cognitive dysfunction (POCD) has been difficult to identify.

Methods. A prospective randomized controlled trial was undertaken in elderly patients undergoing extracorporeal shock wave lithotripsy (ESWL). Between 2005 and 2011, 2706 individuals were screened to recruit 100 eligible patients. Patients were randomly assigned to receive general or spinal anaesthesia alone. A battery of eight neuropsychological tests was administered before operation and at 7 days and 3 months after operation. The reliable change index was used to calculate the incidence of POCD. Intention-to-treat analysis was used to compare rates of POCD.

Results. Futility analysis led to stopping of the trial after recruitment of 100 patients. Fifty patients were randomly assigned to general anaesthesia, and 48 patients to spinal anaesthesia without sedation or postoperative opioids. At 3 months, POCD was detected in 6.8% (95% confidence interval (CI): 1.4–18.7%) of patients in the general anaesthesia group and 19.6% (95% CI: 9.4–33.9%) in the spinal group (P = 0.07). At 7 days after operation, the incidence of POCD was 4.1% (95% CI: 0.5–14%) in the general anaesthesia group and 11.9% (95% CI: 4.0–26.6%) in the spinal group (P = 0.16).

Conclusions. We found no significant difference in the rates of POCD when comparing general anaesthesia with spinal anaesthesia, suggesting that the surgical or procedural process itself may contribute to the development of POCD.

Clinical trial registration. Australian Clinical Trials Registry number ACTRN12605000150640.

Keywords: cognition; general anaesthesia; postoperative cognitive dysfunction; spinal anaesthesia

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Postoperative cognitive dysfunction (POCD) is a decrease in cognition measured by neuropsychological tests after anaesthesia and surgery. It is difficult to separate the effects of surgery from anaesthesia because the administration of general anaesthesia without surgery poses ethical problems, and surgery without anaesthesia is unacceptable.

In the clinical setting, the closest approach to separating general anaesthesia from the surgical process is to administer regional anaesthesia. However, reviews on the incidence of POCD after neuraxial block compared with general anaesthesia have failed to show a decrease in the incidence of POCD.1 2

There are a number of issues with study design which have confounded these studies. First, sedatives may be associated with POCD3 and yet no trial has specifically excluded sedation. Secondly, postoperative analgesics may confound the incidence of POCD, yet previous studies have not documented the use of postoperative opioids. Thirdly, many of the randomized trials were not blinded. Finally, selection and analysis of neuropsychological tests may lead to discrepancies in the calculation of POCD.4

To overcome these issues, we undertook a trial comparing the incidence of POCD in older patients who underwent extracorporeal shock wave lithotripsy (ESWL) under general anaesthesia with patients receiving spinal anaesthesia which specifically excluded sedation and postoperative opioid analgesia. ESWL uses high-energy acoustic shock waves generated outside the...
body to break stones in the kidney. The procedure is painful and requires either intense analgesia or anaesthesia and represents a surgical stress without a surgical incision. At our institution, we routinely administer either general or spinal anaesthesia. Studying POCD after ESWL offers several unique advantages: the procedure can be performed equally well under general or spinal anaesthesia; when performed under spinal anaesthesia co-administration of sedation is not necessary; and postoperative pain is minimal allowing management with simple oral analgesics, obviating the confounding factor of postoperative opioids. It is therefore an ideal proxy for open surgical procedures because there is no incision to create either anxiety or intense postprocedural pain. Consequently, patients are more willing to forgo sedation than during an open surgical incision.

We hypothesized that the incidence of POCD would be less in patients receiving spinal anaesthesia (without sedation or postoperative opioids) than general anaesthesia. The aim of this investigation was to compare the incidence of POCD after a surgical procedure (ESWL) receiving either general or spinal anaesthesia alone.

Methods

This trial was a single-centre prospective randomized controlled trial in patients undergoing ESWL at St Vincent’s Hospital Melbourne, Australia, between 2005 and 2011 (ACTRN 12605000150640). The primary outcome was the incidence of POCD at 3 months. The secondary outcome was the incidence of POCD at 7 days. Institutional Human Research Ethics Committee approval was granted and written informed consent obtained from all patients.

Eligible patients were aged ≥55 yr undergoing ESWL who had no contraindication to neuropsychological testing and resided in accessible proximity to the hospital to allow home assessments. Exclusion criteria were pre-existing neurological disease, Mini-Mental State Examination score ≤25, anticipated difficulty with neuropsychological assessment, contraindications to general or spinal anaesthesia, and associated medical problems.

A non-treatment control group was recruited as part of the Anaesthesia Cognition Evaluation study (ACTRN: 12607000049471) which investigated cognition after total hip joint replacement. All control participants had hip osteoarthritis typically requiring analgesics, and thus provided a suitable control group for study patients with renal stones who also often needed analgesics. These individuals met similar inclusion and exclusion criteria and underwent the same neuropsychological tests administered by a trained interviewer blinded to the patient’s anaesthetic. Testing was done at baseline during the week before ESWL, and at 7 days and 3 months afterwards. All testing was done at the patients’ home to provide a stress-free, reproducible environment.

The test battery consisted of the Consortium to Establish a Registry for Alzheimer’s Disease Auditory Verbal Learning test (CERAD-AVLT), Digit Symbol Substitution test, Trail Making test parts A and B, Controlled Oral Word Association Test (COWAT), Semantic Fluency test, and the Grooved Pegboard test (dominant and non-dominant hands). Parallel forms were administered for the CERAD-AVLT and all the tests were administered in the same order. The National Adult Reading Test was administered at the baseline assessment to estimate intelligence quotient (IQ).

Visual analogue scales were used to assess anxiety, depression, and fatigue at each testing time.

Absolute test scores were reversed for timed tasks so that a decrease implied cognitive decline for every test.

The reliable change index (RCI) was used to calculate the incidence of POCD. RC1 was determined by subtracting the baseline score \(X_1\) from the score at 7 days or 3 months after ESWL \(X_3\), giving \(\Delta X\) for each individual participant for a given task. The mean expected change for the controls \(\Delta_{c}\), was then subtracted from this, removing any time or practice effect. This score was then divided by the \(SD\) for the change in test results of the control group \(SD(\Delta_{c})\), controlling for the expected variability. These scores were then used to create a combined test score \(Z_{combined}\) using the sum of 2 scores for each test \((\sum Z_{a,b,c,d,etc})\) divided by the \(SD\) of this summation in the control group \(SD(\sum Z_{control})\). POCD was defined in an individual when their RCI score was less than or equal to \(-1.96\) on \(>2\) tests, and/or their combined \(Z\)-score was less than or equal to \(-1.96\).

Primary analysis was by intention-to-treat. A secondary per-protocol analysis was also performed.

Power calculations were based on an incidence of POCD at 3 months in older patients of 12% and an assumption that avoidance of centrally acting agents would decrease the
incidence to 1% approximating the incidence of 0% at 3 months seen in the control group\(^{16}\) (consistent with 0% in a normal group of subjects). Two equal groups of 96 would be required to detect a significant difference with a power of 0.80 at the 0.05 significance level.

At 50% recruitment, a futility analysis was undertaken\(^{15}\) \(^{16}\) using a transformed Z-value (\(8\)-value) to calculate conditional power. The following formulae were used to estimate conditional power:

\[
CP(\theta) = 1 - \Phi\left(\frac{Z_{\alpha/2} - B(t) - \theta(1 - t)}{\sqrt{1 - t}}\right)
\]

\[
\theta = \sqrt{N} \frac{X_i - Y_m}{2S_n} = \sqrt{N} \frac{\Delta}{2}
\]

\[
B(t) = Z_n \sqrt{t}
\]

\[
\Delta = \frac{\bar{X} - \bar{Y}}{S}
\]

where \(t\) is the proportion of patients recruited to date (\(N/n\)); \(N\) the patients recruited to Group \(x\); \(m\), patients recruited to Group \(y\).

Group comparisons were made using unpaired \(t\)-tests for continuous variables and \(\chi^2\) or Fisher’s exact test for dichotomous variables. The type I error rate was controlled using the Holm–Bonferroni step-down procedure for multiple comparisons.\(^{17}\)

Associations were determined using univariable analysis and multivariable logistic regression and intention-to-treat, with a probability value of \(<0.2\) set for entry into the multivariable regression models.

Statistical analysis was performed using STATA (Ver. 11.0 Stata Corporation, College Station, TX, USA). A probability value of \(<0.05\) was taken to indicate statistical significance. Exact binomial confidence intervals were calculated in STATA using the Clopper–Pearson interval.

**Results**

Screening of 2706 individuals for ESWL resulted in 98 patients for randomization (Fig. 1). Recruitment was slow because of geographic, language, and medical exclusions and a reluctance to have a spinal anaesthetic without sedation.

No interim analysis was planned, but the need became evident because of slow recruitment.\(^{18}\) At 50% recruitment, a futility analysis was conducted which determined that stochastic curtailment of this study was warranted based on conditional power of data collected to date of \(n (90) = 0\).

We selected 26 control individuals who were matched for age (a known association of POCD).\(^{19}\)

Of the 98 study patients, 50 were randomized to receive general anaesthesia and 48 to receive spinal anaesthesia (Fig. 1). Ultimately, 50 patients received general anaesthesia and 42 received the prescribed spinal anaesthetic protocol.

Five patients were admitted overnight, four in the spinal group (three with urinary retention and one with ureteric pain) and one in the general anaesthesia group (social reasons). None of these patients satisfied the criteria for POCD at either time point.

The mean procedure duration was 45.7 (11.8) min [general: 43.5 (8.6) vs spinal: 47.9 (14.1) min; \(P = 0.07\)].

The control individuals had a higher IQ than the 98 study patients (adjusted \(P < 0.01\)) and performed better than the study patients at baseline in all tests. This was statistically significant for COWAT (adjusted \(P < 0.01\)) and CERAD-A VLT (adjusted \(P = 0.03\)). There was no apparent difference between the general anaesthesia and spinal groups in patient characteristics and medical history (Table 1).

The results of neuropsychological testing between the general and spinal anaesthesia groups on individual tests at baseline indicate that there were no significant differences between the groups (Table 2).

When analysed by intention-to-treat, there was no significant difference in the incidence of POCD between the general anaesthesia and spinal groups. At 3 months, the overall incidence of POCD was 13.6% (12/90) comprising 6.8% (3/44) [95% confidence interval (CI): 1.4–18.7%] in the general anaesthesia group and 19.6% (9/46) (95% CI: 9.4–33.9%) in the spinal group (\(P = 0.07\)) (95% CI for difference: –0.8%, 26.5%).

At 7 days after operation, the incidence of POCD was 7.7% (7/91) comprising 4.1% (2/49) (95% CI: 0.5–14%) in the general anaesthesia group and 11.9% (5/42) (95% CI: 4.0–26.6%) in the spinal group (\(P = 0.16\)) (95% CI for difference –3.3%, 19.1%).

Per-protocol analysis at 3 months showed a significantly increased incidence of POCD in the spinal group. The overall incidence was 14.0% (12/85), comprising 6.8% (3/44) (95% CI: 1.4–18.7%) for the general anaesthesia group and 22.9% (9/41) (95% CI: 10.6–37.6%) for the spinal anaesthesia group (\(P = 0.04\)) (95% CI for difference 0.5%, 29.9%).

Per-protocol analysis at 7 days showed an incidence of POCD of 8.0% (7/87), comprising 4.1% (2/49) (95% CI: 0.5–14.0%) for the general anaesthesia group and 13.2% (5/38) (95% CI: 4.4–28.1%) for the spinal anaesthesia group (\(P = 0.12\)) (95% CI for difference –3.0%, 21.2%).

The results of univariable predictors for POCD with \(P < 0.2\) are shown in Table 3. After multivariable analysis, age and fatigue remained associated with POCD at 7 days but were no longer associated at 3 months.

**Discussion**

In this prospective randomized controlled trial comparing older patients undergoing ESWL, comparing general anaesthesia with spinal anaesthesia, the latter without sedation or postoperative opioids, we were unable to demonstrate a difference between groups in the incidence of POCD at 7 days or 3 months. A secondary per-protocol analysis found that the incidence of POCD at 3 months was significantly higher in the spinal group. Spinal anaesthesia is associated with an incidence of POCD 3 months after ESWL that is at least comparable with that seen after general anaesthesia.

It is difficult to recruit patients to surgical studies in which they are offered spinal anaesthesia without the option of sedation. This difficulty is evidenced by prior studies of which none excluded i.v. sedation, confounding any conclusion on the part played directly by the surgery in contributing to POCD. Indeed, the current study took 6 yr to recruit 100 patients.
2706 patients screened

915 patients eligible

758 patients sent letters and contacted by phone

128 patients verbally consented

100 patients recruited to study

98 patients randomized

Allocated to general anaesthesia (n=50)

Received allocated treatment (n=50)

Day 7—Unable to follow-up (n=1)
Too unwell for testing: 1

Day 7—Analysis
Intention to treat: n=49
Per protocol: n=49

Month 3—Unable to follow-up (n=6)
Withdraw consent: 2
Patient unwell: 3 N not contactable: 1

Month 3—Analysis
Intention to treat: n=44
Per protocol: n=44

Allocated to spinal anaesthesia (n=48)

Received allocated treatment (n=42)
Did not receive allocated intervention (non-protocol: n=6)
Received general anaesthesia: 3
Received sedation: 3

Day 7—Unable to follow-up (n=6) (includes 2 non-protocol patients)
Could not be contacted: 2 Withdrew consent: 1 Too unwell for testing: 3

Day 7—Analysis
Intention to treat: n=42
Per protocol: n=38

Month 3—Unable to follow-up (n=2)
(includes 1 non-protocol participant)
Withdraw consent: 1 Patient unwell: 1

Month 3—Analysis
Intention to treat: n=46
Per protocol: n=41

Fig 1 Study flow.
The slow recruitment rate led us to undertake a futility analysis resulting in stochastic curtailment.20 Table 4 demonstrates the conditional power at several data points and reveals that conditional power was very low from early recruitment. This information of the data trend, together with a conditional power, indicated that continuation of the study would be futile.

This study was designed to show a greater incidence of POCD after general anaesthesia (superiority study). Despite the finding that spinal anaesthesia led to a higher incidence of POCD at 3 months using per-protocol analysis, we cannot make any conclusions regarding a lower incidence of POCD after general anaesthesia. The results do, however, provide pilot data to inform a study designed to investigate a decreased incidence of POCD after general anaesthesia compared with spinal anaesthesia.

This study demonstrates that POCD occurs after surgical treatment in the absence of centrally acting drugs. The result has important implications for the understanding of the mechanisms underlying POCD and cognitive decline in the elderly in general.

Using ESWL as the procedure provided a unique clinical platform. Since spinal anaesthetic agents are confined to a fixed level in the spinal cord,21 and action on the central nervous system above this level is unlikely, any effect on the brain (including POCD) must result from some mechanism other than the direct effects of centrally acting drugs. It is unlikely that trace concentrations of local anaesthetics affect the brain in adults. The results imply that even in the absence of anaesthetic agents, surgical procedures or perioperative stress can lead to POCD.

This platform does not allow conclusions to be drawn about the converse, the effects of anaesthetic agents in the absence of surgery. There is clinical evidence that increased depth of anaesthesia may be associated with an increased incidence of POCD,22 although others have failed to confirm this.23

### Table 1: Patient characteristics and medical history. Data are mean (o) or number (%) except age reported as mean (range). Adjusted P-value is based on the Holmes–Bonferroni correction for multiple comparisons. GA, general anaesthesia; IQ, intelligence quotient

<table>
<thead>
<tr>
<th></th>
<th>GA (n = 50)</th>
<th>Spinal (n = 48)</th>
<th>Controls (n = 26)</th>
<th>GA vs controls, adjusted P-value</th>
<th>Spinal vs controls, adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.9 (55–78)</td>
<td>66.9 (56–81)</td>
<td>68.1 (60–75)</td>
<td>0.04</td>
<td>1.00</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>41/9</td>
<td>37/11</td>
<td>8/18</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.4 (8.3)</td>
<td>171.9 (7.5)</td>
<td>167.2 (8.4)</td>
<td>0.32</td>
<td>0.18</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85.8 (12.8)</td>
<td>84.8 (14.4)</td>
<td>78.4 (14.3)</td>
<td>0.18</td>
<td>0.56</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29.2 (3.8)</td>
<td>28.1 (4.4)</td>
<td>28.1 (5.1)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (24%)</td>
<td>15 (33%)</td>
<td>1 (4%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (59%)</td>
<td>21 (47%)</td>
<td>16 (62%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
<td>2 (8%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>5 (10%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>History of smoking</td>
<td>39 (78%)</td>
<td>28 (61%)</td>
<td>13 (50%)</td>
<td>0.32</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>20 (42%)</td>
<td>21 (49%)</td>
<td>14 (54%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>109.7 (10.1)</td>
<td>105.6 (9.7)</td>
<td>116.7 (18.9)</td>
<td>0.32</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

### Table 2: Neuropsychological testing of participants and controls at baseline. Data are mean (o). Tests are: CERAD-AVLT, Consortium to Establish a Registry for Alzheimer’s Disease Auditory Verbal Learning Test; DSST, Digit Symbol Substitution Test; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; COWAT, Controlled Oral Word Association Test; CERAD, Consortium to Establish a Registry for Alzheimer’s Disease-semantic fluency (animals); GPD, Grooved Peg Board Test, Dominant; GPND, Grooved Peg Board Test, Non-dominant. Adjusted P-value is based on the Holmes–Bonferroni correction for multiple comparisons

<table>
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<th>GA vs controls, adjusted P-value</th>
<th>Spinal vs controls, adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERAD-AVLT (n)</td>
<td>17.5 (4.5)</td>
<td>16.9 (3.6)</td>
<td>18.5 (3.7)</td>
<td>0.43</td>
<td>0.99</td>
<td>0.35</td>
</tr>
<tr>
<td>TMTA (s)</td>
<td>53.3 (22.7)</td>
<td>54.7 (22.3)</td>
<td>45.7 (14.2)</td>
<td>0.76</td>
<td>0.50</td>
<td>0.35</td>
</tr>
<tr>
<td>TMTB (s)</td>
<td>121.7 (50.9)</td>
<td>131.1 (62.5)</td>
<td>95.3 (44.9)</td>
<td>0.41</td>
<td>0.18</td>
<td>0.07</td>
</tr>
<tr>
<td>DSST (n)</td>
<td>36.5 (13.1)</td>
<td>36.4 (12.3)</td>
<td>41.4 (10.0)</td>
<td>0.97</td>
<td>0.50</td>
<td>0.35</td>
</tr>
<tr>
<td>COWAT (n)</td>
<td>31.8 (11.8)</td>
<td>32.1 (11.9)</td>
<td>41.8 (13.9)</td>
<td>0.89</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>CERAD-fluency (n)</td>
<td>17.7 (4.7)</td>
<td>17.6 (4.7)</td>
<td>20.7 (4.9)</td>
<td>0.85</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>GPD (s)</td>
<td>87.5 (18.1)</td>
<td>93.3 (27.6)</td>
<td>84.1 (15.2)</td>
<td>0.22</td>
<td>0.99</td>
<td>0.35</td>
</tr>
<tr>
<td>GPND (s)</td>
<td>95.8 (27.6)</td>
<td>108.9 (56.1)</td>
<td>93.8 (18.6)</td>
<td>0.15</td>
<td>0.99</td>
<td>0.35</td>
</tr>
</tbody>
</table>
If anaesthetic agents do contribute to POCD, the effect may be subsumed within the effects of surgery because the incidence was not greater in subjects receiving general anaesthesia.

Previous studies comparing the incidence of POCD after general vs spinal anaesthesia have not specifically excluded sedation intraoperatively or analgesia after the operation. The largest of these trials enrolled 428 patients and found an incidence of POCD at 3 months of 14.3% (95% CI: 9.5–20.4%) after general anaesthesia which was not significantly different from 13.9% (95% CI: 9.0–20.2%) after regional anaesthesia, $P=0.93$.24 However, 37% of patients in the regional group received i.v. propofol sedation, and centrally acting postoperative analgesia was not restricted. In spite of these shortcomings, the incidence of POCD was not statistically different, indicating POCD may occur in the absence of general anaesthesia. This earlier study, like the present study, had slow recruitment and additionally required high patient numbers because power was based on a 5% incidence of POCD in the spinal group. Other smaller studies have all failed to show a difference, although none has restricted i.v. sedation or postoperative analgesia.12

A possible mechanism may include the inflammatory response, which is associated with surgery and also follows ESWL. After ESWL, tumour necrosis factor-$\alpha$ has been shown to increase in the urine in animal models25 and serum interleukin-6 increases in humans.26 Associations between surgery, inflammation, and cognitive dysfunction have been extensively demonstrated in animal models.27–29 Vacas and colleagues30 have recently reviewed the mechanisms by which peripheral tissue injury resulting from surgical trauma can lead to neuroinflammation and POCD. If inflammation is implicated, the results may be generalizable to other forms of surgery.

The overall incidence of POCD at 3 months of 13.6% is consistent with other studies of major non-cardiac surgery.1 13 The results are consistent with recent data which indicate that POCD at 3 months occurs after other non-invasive interventions such as cardiac angiography (21% [95% CI: 15–28%]) at rates indistinguishable from total hip joint replacements [16% (95% CI: 11–23%)] or cardiac surgery [16% (95% CI: 15–21%)].14

A weakness in the study is the small sample size, but excluding sedation during surgery makes such a clinical trial difficult. Although the small numbers led to wide confidence intervals,
futility analysis indicated that the results would not be significant even at full recruitment. Nevertheless, the findings could be explained by type 2 error. Although the control group was matched for age, they did have a higher IQ (and also performed statistically better than the study patients on two neuropsychological tests). We have previously noted that volunteers have a higher IQ than study patients. However, there was no significant difference between the general anaesthesia and spinal group in age or IQ. Finally, although spinal anaesthetics are reported to afect cortical activity, this is believed to be due to diminished afferent activity, rather than a direct action of trace concentrations of local anaesthetics acting on the brain. We cannot discount that the CSF circulation delivered trace levels of bupivacaine to the brain, although there is currently no evidence to support this.

In summary, by uncoupling the surgical procedure from anaesthesia, we have shown that POCD follows ESWL in older patients who received no centrally acting drugs. The results provide supportive evidence that POCD may be the direct consequence of healthcare interventions other than centrally acting anaesthetic agents.

Authors’ contributions
B.S.S., L.A.E., and D.A.S.: design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; drafting of the manuscript. L.A.E.: statistical analysis.

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Declaration of interest
None declared.

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