Comparison of two patient-controlled analgesia techniques on neuropsychological functioning in the immediate postoperative period

Benzion Beilin,1 Dan Hoofien,2 Ravit Poran,2 Inbal Gral,2 Galina Grinevich,1 Berta Butin,1 Eduard Mayburd,1 and Yehuda Shavit2

1Department of Anesthesiology, Rabin Medical Center, Hasharon Hospital, Petah Tiqva, Israel
2Department of Psychology, The Hebrew University, Jerusalem, Israel

Pain may contribute to cognitive decline, which is a common complication in the early postoperative period. We compared the effects of two common pain management techniques, intravenous patient-controlled analgesia (PCA-IV) and patient-controlled epidural analgesia (PCEA), on cognitive functioning in the immediate postoperative period. Patients hospitalized for elective surgery were randomly assigned to one of the treatment groups (30 patients per group). A battery of objective, standardized neuropsychological tests was administered preoperatively and 24 hours after surgery. Pain intensity was also evaluated. Nonoperated volunteers served as controls. Patients of the PCA-IV group exhibited significantly higher pain scores than did patients of the PCEA group. PCA-IV patients exhibited significant deterioration in the postoperative period in all the neuropsychological measures, while the PCEA patients exhibited significant deterioration only in one cognitive index, compared to controls.

Keywords: Cognitive function; Local anaesthetics; Opiates; PCA-IV; PCEA; Postoperative pain.

INTRODUCTION

The early postoperative period (5–7 days) is associated with a cognitive decline, characterized by impairment in memory and attention function, psychomotor dysfunction, and confusion. Multiple risk factors appear to be involved in the development of postoperative cognitive changes, many of which cannot be altered, such as age, coexisting diseases, lower preoperative cognitive status, and lower education level (Wu, Hsu, Richman, & Raja, 2004). Of the intraoperative factors, type of surgery (especially cardiac) and extended duration of anesthesia have been associated with increased incidence of postoperative cognitive dysfunction (Arrowsmith, Grocott, Reves, & Newman, 2000; Moller et al., 1998). It has been argued that the trauma of surgery is a more important factor than any modifiable aspect of the anesthetic procedure. Most studies have not demonstrated a difference in cognitive function between intraoperative general anesthesia and regional anesthesia (Wu et al., 2004).

Among other factors, postoperative pain, which might be modified by the type of pain management, has been associated with a higher incidence of postoperative cognitive decline (Duggleby & Lander, 1994; Mann et al., 2000). Two common postoperative pain management techniques, intravenous patient-controlled analgesia (PCA-IV) versus patient-controlled epidural analgesia (PCEA), which are based on different drugs and routes of administration, may impact cognitive function. PCEA, mainly based on local anesthetics...
with supplementary low doses of opiates, has been reported to attenuate increased risk for cognitive impairment by providing improved postoperative pain control, decreasing respiratory complications, and minimizing the systemic effects of opiates (Block et al., 2003; Mann et al., 2000; Wu et al., 2005). In comparison, PCA-IV is based on parenteral administration of opiates, which are likely to cause cognitive impairment, particularly in opiate-naïve patients (Ersek, Cherrier, Overman, & Irving, 2004).

Postoperative cognitive dysfunction is commonly assessed during the first postoperative week (Days 5–7) and often after extended postoperative periods (months to years). Recent reports demonstrate that neuropsychological testing could be administered and completed within 18–24 hours of surgery, including following cardiac surgery (Duggleby & Lander, 1994; Rohan et al., 2005; Silbert et al., 2001). Since postoperative pain may be a risk factor for cognitive decline, and since most intensive postoperative pain is usually experienced in the first 24–48 hours following surgery, in the present study we compared the effects of two pain management techniques on neuropsychological functioning within 24 hours of surgery. Patients were randomly assigned to one of two postoperative pain management groups: PCA-IV or PCEA. A battery of neuropsychological tests was administered before and 24 hours following surgery. The battery consisted of a set of objective, standardized tests measuring basic cognitive abilities that were previously reported to be sensitive to pain: focused attention, working memory, and processing speed (Eccleston, 1995; Eccleston & Crombez, 1999). The effects of repeated measures were controlled for by comparing the performance of the patient groups with that of nonoperated controls who performed the same tests twice, 24 hours apart.

**MATERIALS AND METHODS**

**Participants**

A total of 82 patients (45 females, 37 males), aged 29–72 years, of American Society of Anesthesiologists’ (ASA) physical status classification I–III (from Class I–healthy patient, no medical problem, to Class III–severe systemic disease, but not incapacitating), hospitalized for elective surgery, were recruited for this study (see Table 1). Approval from the Hospital Human Studies Committee and informed consent were obtained from the patients. Inclusion criteria included fluency in Hebrew, the absence of serious hearing or vision impairment that would preclude neuropsychological testing, and patients' consent to random assignment to either treatment group. Exclusion criteria were history of head trauma, neurological diseases, alcoholism, drug abuse, and consumption of psychotropic drugs or antidepressants. Immediately prior to surgery, patients were assigned to one of two experimental groups: PCA-IV or PCEA. A battery of neuropsychological tests was administered before and 24 hours following surgery. The battery consisted of a set of objective, standardized tests measuring basic cognitive abilities that were previously reported to be sensitive to pain: focused attention, working memory, and processing speed (Eccleston, 1995; Eccleston & Crombez, 1999). The effects of repeated measures were controlled for by comparing the performance of the patient groups with that of nonoperated controls who performed the same tests twice, 24 hours apart.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>PCA-IV</th>
<th>PCEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>10/10</td>
<td>16/14</td>
<td>17/13</td>
</tr>
<tr>
<td>Age</td>
<td>53.0 (1.3)</td>
<td>53.1 (1.9)</td>
<td>58.0 (2.0)</td>
</tr>
<tr>
<td>Education</td>
<td>13.7 (0.5)</td>
<td>13.4 (0.6)</td>
<td>12.0 (0.6)</td>
</tr>
<tr>
<td>Weight</td>
<td>77.1 (3.3)</td>
<td>71.7 (3.2)</td>
<td>75.2 (2.7)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General surgery</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Gynecology</td>
<td>12</td>
<td>9</td>
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</tr>
<tr>
<td>Urology</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Orthopedics</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total (N)</td>
<td>20</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Surgery duration</td>
<td>95 (6.6)</td>
<td>109 (10.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Notes.** Values are means (SEM). The three study groups did not differ in any of the characteristics. PCA-IV = intravenous patient-controlled analgesia. PCEA = patient-controlled epidural analgesia.

**Measures**

**Neuropsychological assessment**

A battery of neuropsychological tests was initially administered to the patients during the preoperative evaluation session and was readministered 24 hours after surgery, by the same observer. Control participants received the test battery twice, at a 24-hour interval. The order of administration of the tests was the same at both sessions. The following neuropsychological tests were applied.
Simple eye–hand reaction time (SRT) was used to measure focused attention (Blackburn & Benton, 1955). The SRT task employed in this study is part of the Orientation Remediation Module (Ben-Yishay, Piasetsky, & Rattok, 1987). Purple colored circles, 4 cm in diameter, appear in the center of a laptop screen (IBM, R50e), to which the participant has to respond by pressing the space bar with the dominant hand's index and middle fingers. A warning tone precedes the appearance of each stimulus. The test includes 12 trials with a variable interval of 1–5 s between the warning tone and the stimuli. The mean SRT (in ms) is computed as the average of the 12 trials. The Continuous Performance Test (CPT) is a frequently used measure of sustained attention (Beck, Bransome, Mirsky, Rosvold, & Sarason, 1956; Riccio, Reynolds, Lowe, & Moore, 2002; Spreen & Strauss, 1998). In the present study we used the “numbers cancellation with condition” task of the CPT (Loong, 1988). Random bold green colored single digits (22 points font size) appeared on the center of a laptop screen (IBM, R50e) at a pace of 1 digit per second, for 5 minutes. The participant is instructed to press the keyboard space bar when a previously determined conditioned target digit is presented (the digit 9 following the digit 0), and at the same time to ignore the distracting digits (all other digits, including the digit 9 when not presented after 0). Two scores were extracted from this test: percentage absolute correct response (CPT-%Abs; percentage of the number of correct responses out of possible correct responses); and percentage relative correct response (CPT-%Rel; percentage of the number of correct responses out of the total responses made by the participant). These two scores are considered as robust measures of sustained attention. The Digit Span (DS) subtest of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997) is a commonly used measure of attention span and working memory (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). The participant is required to repeat lists of digits, starting with short list of three and ending with nine digits each. Then, the participant is asked to repeat other lists in backwards order.

In order to cover a wide range of processing-speed abilities, we also measured, in addition to SRT, which is a relatively direct measure of processing speed, the Processing Speed Index (PSI), which involves more complex attention abilities (Lezak et al., 2004). This index is composed of two subtests of the WAIS-III (Wechsler, 1997): (a) The Digit Symbol subtest is a measure of psychomotor speed and conditioned associative learning (Lezak et al., 2004). In this paper-and-pencil subtest, the participant is asked to fill in corresponding graphic symbols under rows of digits, according to a digit symbol model that appears on the top of the page. The subtest score is the number of correct symbols drawn within 120 s. (b) The Symbol Search subtest is a measure of processing speed. The participant has to scan lines of graphic symbols and detect pairs of specific symbols within each line. The score is the ratio of correct symbols detected in the total number of lines completed within two minutes. The participants' scores on the Digit Symbol subtest and Symbol Search subtest were combined together to a PSI score (Wechsler, 1997). In the present study, we used the standard WAIS-III scoring system for these subtests.

**Evaluation of subjective pain**

A 10-cm visual analogue scale (VAS), with endpoints labeled “no pain” and “worst possible pain” was used to assess pain intensity in rest and during coughing every 4 hours, up to 24 hours after completion of surgery. Patients were asked to place a mark on a straight horizontal line to describe the amount of pain they were experiencing. The distance between the end labeled “no pain” and the mark placed by the patient is measured and rounded to the nearest centimeter (Ferrante & VadeBoncouer, 1993).

**Study procedure**

Preoperative evaluation was performed by an anesthesiologist, 3–7 days before surgery. Patients' physical status was assessed; they were familiarized with the VAS scale, and they were instructed on the use of the PCA-IV and PCEA pumps. Additional information, including age, weight, demographic status, and education, were documented for patients who consented to participate in the study. They were then administered the battery of five neuropsychological tests, which was completed within 20 min.

**Anesthesia**

Patients were premedicated with lorazepam (1–2 mg, po) 90 min before induction of anesthesia, followed by 2–3 mg iv midazolam on arrival at the operating theatre. Epidural catheter was placed in patients of the PCEA group via the L2–L4 interspaces and advanced 3–4 cm cephaled. The position of the epidural catheter was tested with 3 ml lidocaine 2%, which was followed by administration of a mixture of 12 ml bupivacaine (0.5%) and fentanyl (50–100 μg), 15–20 min before incision.
General anesthesia was induced in both groups by using fentanyl 2–3 μg/kg, propofol 1.5–2 mg/kg, and vecuronium 0.1 mg/kg iv. Anesthesia was maintained with N₂O, isoflurane, and additional fentanyl. Mean arterial blood pressure was maintained within 20% of baseline values with isoflurane and fentanyl. Patients received upper body forced-air warming, and intravenous fluids were warmed to 37°C.

Postoperative pain management

On arrival to the Post-Anesthesia Care Unit (PACU), patients of the PCA-IV group received a loading dose of morphine (3–4 mg) to relieve the intensity of pain. The PCA-IV pump (Abbott Life Care Infuser, Chicago, IL) was set to deliver 1 mg iv bolus of morphine per demand with a lockout time of 6–8 min and a maximum dose of 25 mg in any 4-hr period, without continuous background infusion. If a patient reported a pain score ≥4 on the VAS, an additional bolus of 1–2 mg iv of morphine was given. Patients of the PCEA group were connected to the PCEA pump (Pain Management Provider, Abbott, Chicago IL), and received 3 ml of 0.1% bupivacaine + 2 μg/ml fentanyl per demand (lockout time 10 min), with continuous background infusion of 6 ml/hr.

The neuropsychological test battery was readministered approximately 24 hours after surgery, within 1 hour following disconnection from the PCA-IV or PCEA pump. VAS was assessed by the anesthesiologist on duty every 4 hours and up to 24 hours postoperatively.

The neuropsychological test battery was also administered twice to control participants within a 24-hr interval.

Statistical analysis

VAS scores were averaged over the first 24-hr period. The cumulative amount of morphine and mixture solution consumed by patients of the PCA-IV and PCEA groups, respectively, were averaged over the first 24-hr period.

Following the standard WAIS-III scoring procedure, scores of three subtests, Digit Span (DS), Digit Symbol, and Symbol Search, were transformed to age-weighted scores (mean = 10, SD = 3). Subsequently, scores of two subtests, Digit Symbol and Symbol Search, were converted into a single Processing Speed Index (PSI; mean = 100, SD = 15).

Thus, the neuropsychological test battery yielded five indices (SRT, DS, PSI, CPT-%Abs, CPT-%Rel) for each patient at each administration time point. Difference scores were computed for each patient (and control participant), by subtracting the postsurgery scores from the presurgery scores. In order to evaluate postoperative cognitive decline Z-scores were computed for each neuropsychological index using the procedure outlined by Rasmussen and colleagues (Rasmussen et al., 2001). Postoperative cognitive decline was determined by subtracting the preoperative scores (X₁) from the postoperative score (X₂; i.e., X₂ − X₁), giving ΔX for each individual participant for a given task. The sign of each difference score (ΔX) was adjusted to assure that in all tests a negative ΔX score corresponded to deterioration. The mean expected change for the controls ΔXc, calculated in the same way as for the patients, was then subtracted from the ΔX of the patients, removing the practice effect. This score was then divided by the standard deviation for the change in test results of the control group, SD(ΔXc), controlling for the expected variability. These individual Z-scores were then used to create a combined test score (Zcombined), using the sum of Z-scores for each test (ΣΖa,b,c,d,etc.) divided by the standard deviation of this summation in the control group, SD(ΣZcontrols). Cognitive decline was then defined as a Zcombined score of less than −2, or two or more Z-scores for single tests of less than −2. This classified cognitive decline on the basis of a substantial failure on two or more tests, or a more pervasive subtle decline across the neuropsychological test battery. This procedure has recently been reported to demonstrate the greatest combination of sensitivity and specificity (Lewis, Maruff, Silbert, Evered, & Scott, 2006).

Data are expressed as mean ± SEM. The Student t test was used to compare two means. Analysis of variance (ANOVA) was used to compare more than two means, with the Bonferroni post hoc test correction. Chi-square was used to compare incidence. All comparisons were two-tailed, and a p value of less than .05 was required to rule out the null hypothesis. Statistical analysis was performed using the SPSS statistical package.

RESULTS

The groups were similar in demographic characteristics, including body weight, age, male-to-female ratio, years of education, type and duration of surgery (Table 1). Averaged over the first 24 hrs postoperatively, patients of the PCA-IV group received 37.9 (±5.03) mg of morphine IV; and patients of the PCEA group received a total volume of 221.5 (±13.13) ml of mixture (0.1% bupivacaine + 2 μg/ml fentanyl).

Postoperative pain

Pain scores reveal similar trends between the measures taken at rest and those during coughing. Av-
aged over the 24-hr period postoperatively, patients of the PCA-IV group exhibited significantly higher VAS scores than did patients of the PCEA group, at rest (1.76 ± 0.146 vs. 0.94 ± 0.116), \( t(58) = 4.38, p < .0001 \), or during coughing (2.81 ± 0.207 vs. 1.77 ± 0.185), \( t(58) = 3.75, p < .0001 \), respectively. The last VAS measures were taken at 24 hours postoperatively, just before the postoperative neuropsychological testing. At this time point, VAS scores were significantly different between the two analgesic treatment groups, both at rest (1.5 ± 0.23 and 0.8 ± 0.19 for PCA-IV and PCEA), \( t(58) = 2.30, p < .025 \), or during coughing (2.30 ± 0.30 and 1.40 ± 0.26, respectively), \( t(58) = 2.25, p < .028 \) (Figure 1).

**Neuropsychological tests**

The results refer to five measures: SRT, CPT-%Abs, CPT-%Rel, DS, and PSI.

Table 2 presents baseline (Test 1), postoperative (Test 2), and difference (Test 2 – Test 1) scores for each study group. To avoid multiple statistical analyses on the same data, only baseline scores were statistically analyzed in this table. Baseline scores (Test 1) of the three groups did not differ for the SRT, CPT-%Rel, DS, and PSI measures (Table 2). Significant differences were revealed among the groups only in the CPT-%Abs measure, \( F(2, 77) = 5.19, p < .008 \). Post hoc Bonferroni tests revealed significantly lower CPT-%Abs baseline score in the PCEA group than in the PCA-IV (\( p < .012 \)) and control (\( p < .005 \)) groups.

Since both CPT-%Abs and CPT-%Rel are measures of sustained attention and were significantly correlated in our sample (\( r = .673, .817, .764 \), for Test 1, Test 2, and difference scores, respectively, \( N = 80, p < .0001 \)), since no differences between the groups were observed in the CPT-%Rel measure at both test times, and in order not to include redundant data in the overall analysis, the CPT-%Rel measure was not included in further analyses. Thus, the following Z-scores refer to four measures: SRT, CPT-%Abs, DS, and PSI.

Examining the Z-scores computed for each individual measure, we find that in three out of the four measures, PSI, SRT, and CPT-%Abs, the averaged Z-scores of the PCA-IV group were less than \(-2\), whereas in the PCEA group the averaged Z-scores of no measure fell below \(-2\) (Table 3). Comparing the Z-scores among the study groups, the PCA-IV group exhibited significant deterioration in the postoperative period compared with controls in all the neuropsychological measures and compared with the PCEA group in the CPT-%Abs measure (Bonferroni tests; Table 3). The postoperative performance of the PCEA group was significantly deteriorated compared to that of controls only in the PSI index (Table 3). The combined Z-score revealed significantly deteriorated performance in the PCA-IV group compared to both the control and PCEA groups (Bonferroni: \( p < .000, p < .015 \), respectively). The incidence of patients with a combined Z-score of less than \(-2\), or two or more Z-scores for single tests of less than \(-2\), was 25 out of 30 in the PCA-IV group, and 14 out of 30 in the PCEA group,
χ²(1) = 8.86, p < .003. No participant of the control group exhibited a Z-score of less than −2, or two or more Z-scores for single tests of less than −2 (the value −2 was chosen because only 2.5% of the participants on the standardized scores were expected to have a Z-score of less than −2).

Significant correlations were revealed between the combined Z-score and VAS at 24 hours postoperatively, both at rest (r = −.32, N = 60, p < .011) and during coughing (r = −.35, N = 60, p < .006), suggesting an interaction between postoperative pain and neuropsychological function.

**TABLE 2**
Baseline, postoperative, and difference scores for each neuropsychological test by the three study groups

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>Test 1 (Baseline)</th>
<th>Test 2 (Postoperative)</th>
<th>Test 2 – Test 1 (Difference score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRT</td>
<td>277.15 (17.96)</td>
<td>260.30 (13.45)</td>
<td>−16.85 (11.02)</td>
</tr>
<tr>
<td>CPT-%Abs</td>
<td>96.00 (0.94)</td>
<td>96.60 (1.14)</td>
<td>0.60 (1.34)</td>
</tr>
<tr>
<td>CPT-%Rel</td>
<td>96.16 (0.70)</td>
<td>97.28 (0.58)</td>
<td>1.12 (0.66)</td>
</tr>
<tr>
<td>PSI</td>
<td>95.50 (2.25)</td>
<td>100.90 (2.56)</td>
<td>5.40 (1.08)</td>
</tr>
<tr>
<td>DS</td>
<td>9.10 (0.66)</td>
<td>9.75 (0.62)</td>
<td>0.65 (0.24)</td>
</tr>
<tr>
<td>PCA-IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRT</td>
<td>296.87 (17.32)</td>
<td>381.64 (27.28)</td>
<td>84.77 (21.89)</td>
</tr>
<tr>
<td>CPT-%Abs</td>
<td>94.47 (1.43)</td>
<td>82.27 (3.53)</td>
<td>−12.20 (3.18)</td>
</tr>
<tr>
<td>CPT-%Rel</td>
<td>90.55 (2.74)</td>
<td>83.00 (3.89)</td>
<td>−7.55 (3.09)</td>
</tr>
<tr>
<td>PSI</td>
<td>91.03 (2.63)</td>
<td>84.43 (2.28)</td>
<td>−6.60 (1.59)</td>
</tr>
<tr>
<td>DS</td>
<td>8.20 (0.46)</td>
<td>7.43 (0.45)</td>
<td>−0.77 (0.29)</td>
</tr>
<tr>
<td>PCEA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRT</td>
<td>342.86 (19.47)</td>
<td>387.07 (24.29)</td>
<td>44.21 (24.78)</td>
</tr>
<tr>
<td>CPT-%Abs</td>
<td>88.27 (2.29)</td>
<td>85.87 (2.90)</td>
<td>−2.40 (3.08)</td>
</tr>
<tr>
<td>CPT-%Rel</td>
<td>87.37 (2.50)</td>
<td>85.44 (3.06)</td>
<td>−1.93 (3.22)</td>
</tr>
<tr>
<td>PSI</td>
<td>87.43 (2.52)</td>
<td>83.80 (2.35)</td>
<td>−3.63 (1.20)</td>
</tr>
<tr>
<td>DS</td>
<td>7.90 (0.44)</td>
<td>7.50 (0.36)</td>
<td>−0.40 (0.30)</td>
</tr>
</tbody>
</table>

Note. PCA-IV = intravenous patient-controlled analgesia. PCEA = patient-controlled epidural analgesia. SRT = simple reaction time (ms, raw scores); CPT-%Abs = Continuous Performance Test, % of the number of correct responses out of possible correct responses (raw scores); CPT-%Rel = Continuous Performance Test, % of the number of correct responses out of the total made by the participant (raw scores); PSI = Processing Speed Index (based on age-weighted scores of Digit Symbol and Symbol Search tests); DS = Digit Span (age-weighted scores). Values are means (SEM). Difference scores were calculated as the score in the second test (24 hours postoperatively in the PCA-IV and PCEA groups and 24 hours apart in the control group) minus the baseline score. To avoid multiple analyses on the same data, statistical analysis was performed only on baseline scores in this table.

**TABLE 3**
Difference Z-scores of the three study groups

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>Control</th>
<th>PCA-IV</th>
<th>PCEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT</td>
<td>0.00 (0.22)</td>
<td>−2.06 (0.44)a</td>
<td>−1.24 (0.50)</td>
</tr>
<tr>
<td>CPT-%Abs</td>
<td>0.00 (0.22)</td>
<td>−2.14 (0.53)a,b</td>
<td>−0.50 (0.51)</td>
</tr>
<tr>
<td>PSI</td>
<td>0.00 (0.22)</td>
<td>−2.47 (0.33)a</td>
<td>−1.86 (0.25)a</td>
</tr>
<tr>
<td>DS</td>
<td>0.00 (0.22)</td>
<td>−1.30 (0.26)a</td>
<td>−0.96 (0.27)</td>
</tr>
<tr>
<td>Combined Z-score</td>
<td>0.00 (0.22)</td>
<td>−4.23 (0.71)a,b</td>
<td>−2.17 (0.62)</td>
</tr>
</tbody>
</table>

Note. PCA-IV = intravenous patient-controlled analgesia. PCEA = patient-controlled epidural analgesia. The direction of data was corrected to ensure that in all tests (including SRT) a negative change indicated deterioration. For each individual test (see legend of Table 2 for test descriptions) a Z-score was computed: The mean change for the control group was subtracted from difference scores (Test 2–Test 1) to remove expected practice effect, and the result was divided by the standard deviation for the change in the control group to control for the expected variability. Z-scores of the individual tests were used to calculate the combined Z-score (see Materials and Methods section). Values are means (SEM).

aSignificantly different from that of the control group (post hoc Bonferroni test). bSignificantly different from that of the PCEA group (post hoc Bonferroni test).
DISCUSSION

Patients of the PCEA group exhibited diminished decline in neuropsychological functioning 24 hours after surgery, compared to the PCA-IV group. The cognitive performance of patients of the PCA-IV group significantly deteriorated in all four neuropsychological indices compared with the performance of the control group, whereas postoperative neuropsychological performance in the PCEA group exhibited significant deterioration only in the PSI index. Previous studies have indicated that speed of processing is a most sensitive measure, even following very minor and transient neurological insults, such as mild head injury, postconcussive syndrome, and drugs and alcohol abuse (Beumont, Rogers, & Kenealy, 1999, pp. 122–127, 174–180, 582–587). The present finding reveals a postoperative cognitive decline in the PCEA group only in this very sensitive index.

Overall, both pain management techniques provided adequate postoperative analgesia. Statistically, however, PCEA produced better postoperative analgesia than did the PCA-IV technique, confirming our earlier findings (Beilin et al., 2003), as well as those of others (Block et al., 2000; Mann et al., 2000; Wu et al., 2005). The observed correlations between pain experienced by the patient and neuropsychological function at 24 hours postoperatively suggest that patients experiencing less pain exhibit a smaller decline in cognitive function.

Differences in drugs and route of administration between the two pain management techniques may play a major role in postoperative cognitive function. PCA-IV is based on systemic opiates only. Generally, patients receiving chronic oral opiate therapy show no cognitive impairment, whereas parenteral opiates are associated with dose-related cognitive impairment, even in healthy patients (Ersek et al., 2004). It has recently been shown that patients receiving postoperative analgesia by oral opiates are at a lower risk of postoperative cognitive decline than are patients receiving opiates by PCA-IV (Y. Wang, Sands, Vaurio, Mullen, & Leung, 2007). By contrast, PCEA is based on an epidural mixture of local anesthetics and opiates. It has been shown that intraoperative administration of IV local anesthetic (lidocaine) significantly reduced the occurrence of postoperative cognitive dysfunction nine days after coronary artery bypass surgery (D. Wang et al., 2002).

Other factors that may contribute to cognitive differences between the two patient groups are surgery-induced hormonal and neurotransmitter imbalance, and the release of proinflammatory cytokines (Wu et al., 2004). Elevated levels of cortisol may adversely affect mood, sleep, energy, and cognition, in part through modulation of neurotransmitter activity (Kiraly, Ancill, & Dimitrova, 1997). We have recently shown that patients treated with PCEA exhibited diminished postoperative elevation of serum cortisol levels compared with patients treated with PCA-IV (Yardeni et al., 2007). Proinflammatory cytokines, particularly IL-1 and IL-6, are produced and secreted both in the brain and the periphery following exposure to psychological stressors (Watkins, Nguyen, Lee, & Maier, 1999) and have been implicated in stress-induced hormonal, affective, and cognitive effects (Goshen, Yirmiya, Iverfeldt, & Weidenfeld, 2003; Maier, 2003). Surgery-associated tissue injury and stress are also accompanied by elevated levels of proinflammatory cytokines (Watkins, Maier, & Goehler, 1995). We have shown that PCEA-treated patients exhibited attenuated proinflammatory cytokine elevation following surgery compared with PCA-IV patients (Beilin et al., 2003). This latter finding may be related to the local anesthetics used in the PCEA technique, as it has been shown that local anesthetics have systemic anti-inflammatory properties of their own (Hollmann & Durieux, 2000). Thus, it is tempting to speculate that differences in cytokine release may also contribute to the cognitive differences between the two analgesic techniques.

Cognitive decline usually begins immediately after surgery (Silbert et al., 2001), peaks within 3 days (Dyer, Ashton, & Teasdale, 1995), and recovers in most patients by 1 week after the surgery, although in a small number of cases it might still be evident even 1–2 years after surgery (Abildstrom et al., 2000). Patients undergoing surgery report that the most severe pain occurs in the first 24–48 hours postoperatively, which suggests that if the cognitive effect of pain is the goal of the study it should be examined in the immediate postoperative period. Neuropsychological testing in this period is complicated by factors not seen at later testing times, such as residual effects of drugs used during the anesthesia, or current effects of the analgesics. However, there are reasons to obtain cognitive function at an earlier stage, in spite of practical difficulties, including the fact that some deficits may no longer be evident by 3 days postoperatively and the possibility that some intervention, such as effective pain management, might be applied at the first possible opportunity. A recent study (Y. Wang et al., 2007) has corroborated the present findings, stressing the importance of early (24–48 hours) postoperative neuropsychological assessment. Since most surgical patients are...
discharged within a few days of surgery, cognitive decline at the early period may limit their ability to understand how to care for themselves after discharge and may put them at risk for postsurgical complications. This report also argues that pain management is a major risk factor for cognitive decline in the immediate postoperative period.

The present findings clearly indicate that patients treated with PCEA exhibit reduced postoperative pain and attenuated neuropsychological decline in the immediate postoperative period, compared with patients of the PCA-IV group. Further research is required to investigate whether the observed results may extend to a later postoperative time point and may facilitate patient recovery and quality of life later on.

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