Cortical somatosensory evoked potentials (CSEP) allow monitoring of spinal cord function during surgery. Ketamine has been shown to enhance CSEP amplitude, but there is no previous study comparing its effects with those of other anaesthetic regimens. Therefore, we have compared the effects of ketamine with those of fentanyl, both combined with midazolam, on CSEP monitoring during major spine surgery. Twenty patients with normal preoperative CSEP were allocated randomly to a ketamine or fentanyl group. Anaesthesia was induced with ketamine 3 mg kg\(^{-1}\) or fentanyl 6 \(\mu g\) kg\(^{-1}\) i.v., and midazolam 0.3 mg kg\(^{-1}\) i.v in both groups, and maintained with continuous i.v infusion of ketamine 2 mg kg\(^{-1}\) h\(^{-1}\) or fentanyl 3 \(\mu g\) kg\(^{-1}\) h\(^{-1}\), combined in both groups with midazolam 0.15 mg kg\(^{-1}\) h\(^{-1}\) and 60% nitrous oxide in oxygen. CSEP were elicited by tibial posterior nerve stimulation and measured P1 and N1 latencies, and P1-N1 amplitude. CSEP were recorded before and after induction, at 15 min, 1 and 2 h after induction, during skin closure and after removal of nitrous oxide. Both groups were comparable in characteristics, duration of surgery, mean arterial pressure and temperature. CSEP latencies were not significantly affected in either group. CSEP amplitude decreased significantly overtime in the fentanyl group (from mean 2.02 (SEM 0.41) to 0.95 (0.17) \(\mu V\), \(P<0.05\), but not in the ketamine group (from 1.33 (0.36) to 1.05 (0.31) \(\mu V\), ns). Nevertheless, we did not observe any significant differences in amplitudes or latencies between the two groups. The delay in obtaining the first voluntary postoperative motor response was significantly greater in the ketamine group (170 (54) vs 55 (17) min, \(P<0.01\)). Both ketamine and fentanyl allowed us to obtain reliable CSEP during major spine surgery, and there were no significant difference between these two anaesthetic regimens for CSEP monitoring, but a longer delay for voluntary postoperative motor assessment was observed in the ketamine group. (Br. J. Anaesth. 1997; 78: 701–706).

Key words
with abnormal preoperative CSEP were excluded; additional criteria for exclusion were hypertension, coronary artery disease, psychiatric disorders and ASA III or IV status.

ANAESTHESIA TECHNIQUE

Patients received hydroxyzine 1–1.5 mg kg⁻¹ orally 90 min before surgery. Using a random number table, patients were allocated to a ketamine or fentanyl group. Anaesthesia was induced with ketamine 3 mg kg⁻¹ or fentanyl 6 μg kg⁻¹ i.v., combined with midazolam 0.3 mg kg⁻¹ i.v. in both groups. Neuromuscular block for tracheal intubation was produced with vecuronium 0.1 mg kg⁻¹ i.v. Anaesthesia was maintained with continuous i.v. infusion of ketamine 2 mg kg⁻¹ h⁻¹ or fentanyl 3 μg kg⁻¹ h⁻¹, combined with midazolam 0.15 mg kg⁻¹ h⁻¹ and 60% nitrous oxide in oxygen in both groups. After skin closure, nitrous oxide was first removed and after the last CSEP measurement the infusions were discontinued.

Throughout the study the lungs were ventilated mechanically and minute ventilation was adjusted to maintain end-tidal carbon dioxide tension ($E_{CO_2}$) at 4.0–4.8 kPa. Oesophageal temperature was monitored, and hypothermia was prevented using a heating blanket and perfusion warming. Haemodynamic measurements were obtained via an indwelling radial artery catheter connected to a haemodynamic monitor (HP 78354, Hewlett-Packard, Andover, MA, USA). When required, an i.v. bolus of nicardipine 2 mg (Loxen, Sandoz) was administered to maintain mean arterial pressure (MAP) at 60–80 mm Hg to decrease intraoperative bleeding. Haemoglobin concentration was measured during operation using an infrared monitor (HemoCue, Angelholm, Sweden) and was maintained greater than 8 g dl⁻¹ using autologous and homologous blood transfusion, as available.

CSEP RECORDING

CSEP were recorded with a Nicolet compact IV (Nicolet Biomedical Instruments, Madison, WI, USA) and were elicited by alternate right and left lower limb posterior nerve stimulation with subdermal needle electrodes placed on the ankle (frequency 4.3 Hz, duration 150 ms, intensity twice the motor threshold). As regional hypothermia could affect the CSEP, we paid careful attention to covering the lower limbs with a heating blanket. CSEP were recorded simultaneously with transcutaneous scalp Ag–AgCl electrodes (impedance <2 kΩ) located in the medio-central and medio-frontal positions (CZ–F3 in the International 10–20 System). To obtain a better CSEP signal, 500 stimulations were cumulated and averaged every 2 min, using bandpass filters of 10 and 1000 Hz and recorded over a 100-ms time base. At each sample period, CSEP were defined as an increase in latency (P1) or negativity at approximately 40 ms from the time of stimulus, $N1$ = first negative deflection occurring at approximately 50 ms from the time of stimulus. Amplitude (A) was measured from peak to peak of these two deflections.

The CSEP are represented by downward deflections and labelled P (fig. 1). In the same way, negative waves of the CSEP are represented by upward deflections and labelled N (fig. 1). Latencies were measured regarding positivity at approximately 40 ms (P1) and negativity at approximately 50 ms (N1) of the primary cortical peaks from the time of stimulus. Amplitude (A) was measured from peak to peak of these two deflections (fig. 1). CSEP monitoring was recorded continuously by a trained neurophysiologist who was unaware of the anaesthesia technique used. Intraoperative abnormalities of CSEP were defined as an increase in latency (P1 or N1) of at least 10% of previous values (throughout two acquisition periods, 4 min) and a decrease in amplitude of at least 50% of previous values, as reported previously. According to our routine procedure and as recommended previously, a “wake-up” test was required if such abnormalities occurred during a high-risk period of surgery.

MEASUREMENTS

The following variables were measured simultaneously while patients were awake (control period), at the end of induction, 15 min, 1 and 2 h after induction, during skin closure and after removal of nitrous oxide (expired concentration ($E_{N_2O}$) less than 10%): heart rate (HR), MAP, $E_{CO_2}$, $E_{N_2O}$, oesophageal temperature and CSEP. Before and after induction, at the end of surgery and in the recovery room, arterial blood was obtained to measure partial pressure of oxygen ($PaO_2$) (BGElectrolytes Apparatus, Instrumentation Laboratory, Milano, Italy) and haemoglobin concentration (Cobas Argo, Apparatus, Roche, Basle, Switzerland). We also recorded the amount of crystalloids, colloids and blood administered during operation, duration of anaesthesia and surgery, and delay between the end of anaesthesia and the first voluntary postoperative motor response of the lower limbs. To obtain a reliable voluntary motor response of the lower limbs,
Ketamine–midazolam vs fentanyl–midazolam and CSEP

this test was explained to each patient during the preoperative visit, and the postoperative assessment was performed every 15 min in the recovery room by a physician who was unaware of the anaesthesia technique.

STATISTICAL ANALYSIS

Data are expressed as mean (SEM). Comparisons of two means and two percentages were performed using the Student’s t test and Fisher’s exact method, respectively. Comparison of several means was performed using repeated-measure analysis of variance and Newman–Keuls test. All P values were two-tailed and P<0.05 was considered significant. Statistical analysis was performed on a computer using PCSM software (Deltasoft, Meylan, France).

Results

CSEP recording was available and satisfactorily analysed in all patients throughout the study. We did not have to perform a wake-up test, and no neurological complications occurred during or after surgery. We did not observe any undesirable psychomimetic side effects related to ketamine. There were no significant differences between the two groups in age, ASA status, body weight, duration of anaesthesia or surgery, total dose of nicardipine, intrathecal fluids or blood transfusion (table 1). HR was significantly greater in the ketamine group, but MAP, temperature, \( E_{CO_2} \), \( P_{HAO_2} \) and haemoglobin concentration were not significantly different between the two groups (table 2).

CSEP amplitude decreased significantly from induction until the end of surgery in comparison with control values in the fentanyl group (from 2.02 (0.41) to 0.95 (0.17) \( \mu V \), \( P<0.05 \)), but not in the ketamine group (from 1.33 (0.36) to 1.05 (0.31) \( \mu V \), ns). However, there were no significant differences between the two groups (fig. 2). In both groups, we observed no significant increases in CSEP amplitude at the end of surgery after removal of nitrous oxide and there were no significant differences between groups (fig. 2).

Figure 2 Comparison of amplitude of cortical somatosensory evoked potentials in the ketamine (\( n=10 \)) and fentanyl (\( n=10 \)) groups when awake (control (C)), immediately after induction of anaesthesia (Ind.), at 15 min, 1 and 2 h of anaesthesia, during skin closure (Closure) and at the end of anaesthesia with removal of nitrous oxide (i.e. end-tidal nitrous oxide <10%) (End). Data are mean (SEM). \(* P<0.05 \) vs control values. \( P \) values refer to between-group differences.

Table 1 Comparison of the main characteristics in the ketamine and fentanyl groups. Data are mean (SEM or range or number). No significant difference between groups

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Ketamine group (( n=10 ))</th>
<th>Fentanyl group (( n=10 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>53 (22–83)</td>
<td>49 (31–64)</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/3</td>
<td>2/8</td>
</tr>
<tr>
<td>ASA status (I/II)</td>
<td>6/4</td>
<td>7/3</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>64 (3)</td>
<td>60 (4)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>291 (21)</td>
<td>310 (20)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>221 (16)</td>
<td>204 (27)</td>
</tr>
<tr>
<td>Intraoperative crystalloids (ml)</td>
<td>3050 (328)</td>
<td>3050 (189)</td>
</tr>
<tr>
<td>Intraoperative colloids (ml)</td>
<td>650 (130)</td>
<td>425 (167)</td>
</tr>
<tr>
<td>Intraoperative blood transfusion (ml)</td>
<td>780 (323)</td>
<td>870 (343)</td>
</tr>
<tr>
<td>Total dose of nicardipine (mg)</td>
<td>10 (3)</td>
<td>11 (4)</td>
</tr>
</tbody>
</table>

Table 2 Comparison of heart rate (HR), mean arterial pressure (MAP), oesophageal temperature, end-tidal CO₂ concentration (\( E_{CO_2} \)), and partial arterial oxygen pressure (\( P_{HAO_2} \)) in the ketamine (\( n=10 \)) and fentanyl (\( n=10 \)) groups. Data are mean (SEM). \(* P<0.05 \) vs control values; \( \dagger P<0.05 \) vs induction values

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Induction</th>
<th>15 min</th>
<th>1 h</th>
<th>2 h</th>
<th>Skin closure</th>
<th>End</th>
<th>Comparison between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beat min(^{-1}))</td>
<td>Ketamine</td>
<td>89 (4)</td>
<td>93 (5)</td>
<td>90 (4)</td>
<td>80 (6)</td>
<td>80 (5)</td>
<td>78 (4)</td>
<td>76 (4)*</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>88 (5)</td>
<td>77 (6)</td>
<td>69 (5)*</td>
<td>67 (3)*</td>
<td>70 (7)*</td>
<td>84 (8)</td>
<td>81 (9)</td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>Ketamine</td>
<td>103 (3)</td>
<td>99 (13)</td>
<td>95 (4)</td>
<td>91 (5)</td>
<td>80 (4)*</td>
<td>77 (4)*</td>
<td>74 (4)*</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>99 (4)</td>
<td>84 (5)*</td>
<td>82 (9)*</td>
<td>79 (5)*</td>
<td>74 (4)*</td>
<td>77 (4)*</td>
<td>74 (4)*</td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>Ketamine</td>
<td>36.8 (0.1)</td>
<td>36.2 (0.2)*</td>
<td>35.9 (0.2)*</td>
<td>35.2 (0.2)*</td>
<td>35.2 (0.2)*</td>
<td>35.3 (0.3)*</td>
<td>35.3 (0.3)*</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>37.0 (0.1)</td>
<td>36.3 (0.2)*</td>
<td>36.1 (0.2)*</td>
<td>35.6 (0.2)*</td>
<td>35.4 (0.2)*</td>
<td>35.4 (0.3)*</td>
<td>35.4 (0.4)*</td>
<td></td>
</tr>
<tr>
<td>( E_{CO_2} ) (kPa)</td>
<td>Ketamine</td>
<td>4.5 (0.4)</td>
<td>4.4 (0.3)</td>
<td>3.9 (0.1)*</td>
<td>3.9 (0.4)*</td>
<td>3.7 (0.1)*</td>
<td>3.6 (0.1)*</td>
<td>3.6 (0.1)*</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>4.3 (0.3)</td>
<td>4.1 (0.1)</td>
<td>3.9 (0.1)</td>
<td>4.0 (0.1)</td>
<td>3.9 (0.1)</td>
<td>3.6 (0.1)</td>
<td>3.6 (0.1)*</td>
<td></td>
</tr>
<tr>
<td>( P_{HAO_2} ) (kPa)</td>
<td>Ketamine</td>
<td>216 (17)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>203 (28)</td>
<td>ns</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>217 (20)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>218 (43)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g dl(^{-1}))</td>
<td>Ketamine</td>
<td>11.0 (0.5)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>8.9 (0.7)*</td>
<td>ns</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>9.8 (0.2)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>8.0 (0.3)*</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

We found that both ketamine–midazolam and fentanyl–midazolam anaesthesia, with 60% nitrous oxide in oxygen, enabled us to obtain satisfactory CSEP recordings, and we did not observe any significant differences in latencies and amplitudes of CSEP between the two groups. In contrast, recovery was delayed significantly in the ketamine group.

During spine surgery, CSEP monitoring provides sensitive information on spinal cord dysfunction caused by mechanical spinal cord injury, ischaemia, or both.\(^1,2\) In a large multicentre survey, including 51 263 procedures for major spine surgery, Nuwer and colleagues\(^2\) reported that neurological deficits occurred in only 0.55% of patients when CSEP monitoring was performed. To increase the reliability of CSEP recording and monitoring, several independent technical factors should be controlled to decrease false positive and negative rates of spinal injury. First, experience in CSEP monitoring is an important factor, as reported previously.\(^1,2\) In our study, CSEP monitoring was performed by the same neurophysiologist (F. L.) highly trained in intraoperative CSEP monitoring.\(^17\) Second, the early cortical components, P1 and N1, are considered the most reliable waveforms for CSEP recording\(^19\) because their amplitude is greater than that of other peaks and because they exhibit lower variability.\(^9\) Indeed, P1 and N1 components usually exhibit variability less than 30% in amplitude and 1.0 ms in latency.\(^16\) Consequently, in our study, P1 and N1 were analysed to obtain a better signal-to-noise ratio and to increase the reliability of our CSEP recordings. Third, factors other than the anaesthesia technique can affect CSEP recording. These factors are related to spinal cord ischaemia, profound and sustained systemic hypotension,\(^1,2\) severe hypoxia\(^21\) and low packed cell volume with hypovolaemic status.\(^1,20\) In contrast, isovolaemic haemodilution in subjects with normal CSEP, as in our study, does not affect CSEP monitoring.\(^22\) Impairment of CSEP monitoring may be related (mainly latencies rather than amplitudes) to hypothermia in the 25–35 °C temperature range,\(^23\) hypocapnia\(^25\) and hypercapnia.\(^25\) We controlled all of these factors during surgery, including regional limb hypothermia. However, we recorded oesophageal temperature which correlates better with CSEP changes than lower limb muscle temperature.\(^24\) Thus MAP, oesophageal temperature, \(\text{PaCO}_2\), and haemoglobin concentration were maintained within values which enabled CSEP to be monitored satisfactorily throughout the study (table 2). Moreover, there were no significant differences between the two groups for each of these variables (table 2). Lastly, neuromuscular block was produced by vecuronium for tracheal intubation but was not maintained during the study. Neuromuscular block has not been shown to alter CSEP recording.\(^27\)

CSEP may be affected by volatile or i.v. anaesthetics,\(^1,5\) and by their mode of administration (bolus vs continuous).\(^1,7\) To improve CSEP recording and signal-to-noise ratio, some authors have suggested previously that ketamine be used as a
general anaesthetic to increase cortical amplitudes of CSEP produced by peripheral nerve stimulation.\(^{11}\)

In contrast with previous observations, CSEP amplitude in the ketamine group was not increased significantly in our study. This difference may be explained easily. In our study, CSEP monitoring was performed throughout surgery over a long period (more than 2 h) and not only during the first 60 min after induction. As reported previously,\(^{28}\) the time course of anaesthetic effects on CSEP may be prolonged and complex, and to avoid confusing transient CSEP changes with sustained changes, a prolonged study is required. Examination of the results from Schubert, Licina and Lineberry\(^{11}\) shows that the increase in CSEP amplitude was significant only during the first 30 min, immediately after bolus injection of ketamine, and was no longer significant 60 min later in comparison with pre-induction values, with or without exposure to nitrous oxide. To avoid transient CSEP changes, we performed continuous administration of i.v. anaesthetics. Moreover, our results are in accordance with a recent study in humans\(^{29}\) which reported that the amplitude of mid-latency auditory evoked potentials is maintained, and not increased, during ketamine anaesthesia, compared with pre-induction values. It should also be pointed out that CSEP were recorded from the upper and not from the lower limbs in the study of Schubert, Licina and Lineberry.\(^{11}\)

Moreover, as in the studies carried out by Schubert, Licina and Lineberry\(^{11}\) and Schwender and colleagues,\(^{29}\) we did not observe any significant changes in the latencies of P1 and N1 with ketamine, and no significant differences were noted for latencies between the two groups. In summary, there were no significant differences between ketamine–midazolam and fentanyl–midazolam anaesthesia for CSEP variables throughout the study.

The only significant difference between the two groups was a greater delay in obtaining the first voluntary motor response in the recovery room. This suggests that the diagnosis of potential spinal cord dysfunction in the immediate postoperative period should have been delayed. Indeed, rapid postoperative assessment of spinal cord function is important to detect: (1) spinal cord injury limited to motor pathways, thus not detected by CSEP; (2) delayed consequences of intraoperative spinal cord injury; and (3) postoperative spinal cord injury (haematoma). Moreover, because an antagonist of ketamine does not exist, we may speculate that an intraoperative wake-up test could have been easier and more rapid with fentanyl–midazolam anaesthesia than with ketamine–midazolam anaesthesia. This may also be important, because fewer neurological deficits occurred if a wake-up test was performed with CSEP monitoring.\(^{2}\)

There are some limitations of this study. First, some patients scheduled for spine surgery may have abnormal preoperative CSEP. Because we studied patients with normal preoperative CSEP, further studies are thus required to assess the precise effects of ketamine in patients with abnormal preoperative CSEP. Second, the study included only 20 patients, and thus its power may have been too low to detect a significant difference. However, we considered that, if a significant difference does exist, then the magnitude of the difference between the two groups would not be clinically important.

In summary, both ketamine and fentanyl allowed satisfactory CSEP monitoring during major spine surgery, and we found no significant difference in CSEP monitoring between these two anaesthetic regimens. Nevertheless, ketamine was associated with a significant longer delay for first postoperative voluntary motor function assessment and would not allow a rapid peroperative wake-up test. Consequently, there appears to be at present no advantage in the use of ketamine during major spine surgery when CSEP monitoring is required.

**References**


