**Comparison of the effect of propofol and sevoflurane anaesthesia on acute and chronic postoperative pain after hysterectomy**

M. OGURLU*, S. SARI†, M. KÜÇÜK‡, M. BAKI§, B. UĞUR**, Y. E. ESHRAGHI††, F. GALIMBERTI‡‡, A. TURAN§§

*Department of Anesthesiology and Reanimation, Adnan Menderes University, Aydin, Turkey

**SUMMARY**

There is some evidence that propofol may reduce acute postoperative pain; however, the results are inconsistent. Furthermore, there is a paucity of information about the type of anaesthesia and chronic pain. This study was designed to evaluate the hypothesis that propofol reduces acute and chronic postoperative pain compared with sevoflurane. In a randomised, prospective, double-blind trial, we assigned 80 patients having open total abdominal hysterectomy surgery to anaesthesia with either sevoflurane or propofol. Anaesthesia was titrated to clinical needs and bispectral index values to between 40 and 60. Postoperative pain was managed with pethidine and diclofenac. Acute postoperative pain for 24 hours and chronic postoperative pain at one and three months after surgery were evaluated. The Hospital Anxiety and Depression Scale was used to evaluate patient anxiety and depression after one and three months. There were no significant differences between the groups for opioid consumption or opioid-induced side-effects. Pain scores in the first four hours were significantly higher in the sevoflurane group. Persistent surgical pain was observed less frequently (7 out of 40 patients in the propofol group and 21 out of 40 in the sevoflurane group at three months post-surgery, P <0.01) and pain scores were lower at one and three months in the propofol group (0.78±0.55 versus 2.23±0.73 for the sevoflurane group at three months post-surgery, P <0.01). Anxiety and depression scores were significantly lower in the propofol group at three months. In this study, general anaesthesia with propofol was associated with reduced early acute postoperative and persistent pain, compared to sevoflurane-based anaesthesia, among patients undergoing open abdominal hysterectomy.

Key Words: propofol anaesthesia, sevoflurane anaesthesia, postoperative pain, hysterectomy

Significant numbers of patients who undergo surgical procedures each year suffer from moderate to severe pain, regardless of the advances in analgesic techniques. Inadequate treatment of pain results in avoidable suffering and may prolong hospitalisation and increase healthcare costs.

Some studies have verified that general anaesthetic drugs can activate peripheral nociceptive neurons, thus potentially affecting postoperative pain. Clinical trials demonstrate conflicting results—some show that postoperative pain is less following propofol-based anaesthesia compared with volatile-based anaesthesia. Cheng et al reported that patients anaesthetised with propofol had less postoperative pain during the first 24 hours than patients anaesthetised with isoflurane. Others compared the recovery profile of propofol anaesthesia with inhaled anaesthesia and suggested better postoperative analgesia with propofol. Tan et al found that day surgery patients anaesthetised with propofol had less pain than those anaesthetised with sevoflurane, but other studies found no beneficial effect on acute postoperative pain after propofol.

Persistent postoperative pain is defined as incisional pain, after a surgical procedure, that lasts at least three months. It is well established that uncontrolled acute pain after surgery is a risk factor for chronic postoperative pain and, consistent with this, it is suggested that better acute pain control might lead
to lower chronic postoperative pain\(^{12}\). Although the effect of propofol anaesthesia on acute postoperative pain has been studied previously without clear conclusions, there is little information regarding persistent pain. Song et al\(^{11}\) evaluated the effect of propofol anaesthesia on persistent pain after thoracotomy and noted a significant reduction. Persistent pain after thoracotomy may be different to that after other surgery, as a result of greater nerve injury\(^{12,14,15}\). This study was designed to investigate the effect of propofol and inhalational anaesthesia on persistent pain after a different surgical procedure. We tested the hypothesis that propofol anaesthesia would decrease persistent pain after hysterectomy compared with sevoflurane-based anaesthesia. We also tested the hypothesis that acute pain would be less.

**METHODS AND MATERIALS**

With the approval of the Institutional Review Board of Adnan Menderes University in Aydin, Turkey (13.01.2010, protocol number: 2009/00349), and written informed consent, 80 patients undergoing a Pfannenstiel incision for open abdominal hysterectomy and salpingo-oophorectomy were enrolled in this prospective, randomised, double-blind study. Patients were included if they were at least 18 years old, of American Society of Anesthesiologists status 1 to 3 and had no significant cardiovascular or central nervous system disease. A detailed preoperative pain history was obtained, and patients with pre-existing pain syndromes or routinely using medications were excluded. Patients with uterine cancer, renal disease or a history of drug abuse were also excluded.

During the preoperative evaluation and on the day of surgery, prior to anaesthesia premedication, a visual analogue scale (VAS) was explained to all patients. Using a computer-generated randomisation sequence, independent research staff assigned groups immediately prior to entering the operating room. The same surgical team performed all the procedures. The patients and the research staff involved in postoperative assessments were blinded to group allocations. Midazolam 0.07 mg/kg and atropine 0.01 mg/kg were administered intramuscularly 45 minutes before surgery as per institution standard. Intravenous (IV) fentanyl 1 µg/kg was administered prior to surgical incision and repeated as clinically indicated by the anaesthetist who was blinded to study aims and was not involved in data collection. Anaesthetic induction was achieved with 2 to 2.5 mg/kg propofol and 0.1 mg/kg vecuronium, and anaesthesia was maintained using either a propofol infusion (Group P) or sevoflurane (Group S), both titrated to clinical needs and to keep bispectral index values between 40 to 60. Before skin closure, 0.1 mg/kg morphine was given IV and residual neuromuscular blockade was reversed with IV neostigmine 1.5 mg and atropine 0.5 mg. Ondansetron 4 mg IV was administered before extubation for antiemetic prophylaxis. Patients were transferred to the post-anesthesia care unit and VAS pain scores assessed (0=no pain and 10=worst pain imaginable). Pain was assessed while the patient was lying in the bed and

### Table 1

|                          | Group P (n=40) | Group S (n=40) | P Value
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>47.3±8.2</td>
<td>45.0±5.1</td>
<td>0.14*</td>
</tr>
<tr>
<td><strong>ASA status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28 (70%)</td>
<td>33 (82.5%)</td>
<td>0.19*</td>
</tr>
<tr>
<td>2</td>
<td>12 (30%)</td>
<td>7 (17.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Surgical indications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>36</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Treatment resistant menorrhagia</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>72.1±12.8</td>
<td>71.37±13.9</td>
<td>0.82*</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>158.8±3.7</td>
<td>159.1±3.1</td>
<td>0.62*</td>
</tr>
<tr>
<td><strong>Anaesthesia (min)</strong></td>
<td>95.1±21.4</td>
<td>107.6±18.0</td>
<td>0.006*</td>
</tr>
<tr>
<td></td>
<td>[90]</td>
<td>[110]</td>
<td>{-2.86}</td>
</tr>
<tr>
<td><strong>Surgery (min)</strong></td>
<td>83.1±21.7</td>
<td>94.9±18.9</td>
<td>0.01*</td>
</tr>
<tr>
<td></td>
<td>[77.5]</td>
<td>[100]</td>
<td>{-2.62}</td>
</tr>
</tbody>
</table>

Data are represented as number (percentage), mean ± SD or [median]. *chi-square test, \(^*\)Student's t-test, {Wilcoxon test}. ASA= American Society of Anesthesiologists.
PROPOFOL ANAESTHESIA DECREASES POSTOPERATIVE PAIN

**Figure 1:** Incidence of persistent postoperative pain at one and three months in the sevoflurane and propofol groups. *P* <0.05, **P** <0.01. 

**Figure 2:** Persistent postoperative pain after one and three months in the sevoflurane and propofol groups. *P* <0.05, **P** <0.01. VAS=visual analogue scale.

**Figure 3:** Postoperative pain scores at rest over the 0 to 24 hour postoperative period. VAS=visual analogue scale.

**Figure 4:** Postoperative pain scores with movement over the 0 to 24 hour postoperative period. VAS=visual analogue scale.

**Figure 5:** Anxiety scores at one and three months in sevoflurane and propofol groups. *P* <0.05.

**Figure 6:** Depression scores at one and three months in sevoflurane and propofol groups. *P* <0.05.
after sitting up, at 30 minutes and one hour, and later in the ward every four hours. Patients received IV pethidine 0.5 mg/kg and intramuscular diclofenac 75 mg when the VAS score was >4 or when the patient requested an analgesic. After the first 24 hours, oral diclofenac 75 mg was given 12-hourly. Sedation scores were evaluated in the first two hours using the Aldrete scoring system.

Demographic parameters (patient age, sex, height and weight) were recorded at the preoperative evaluation. Vital signs, the Ramsay sedation scale, pain scores during normal breathing at rest and after sitting up, and analgesic use were recorded at 30 minutes and at 1, 4, 8, 12, 16, 20 and 24 hours after surgery. Patients were questioned throughout the postoperative period about the occurrence of any adverse effects, such as nausea and vomiting, constipation, respiratory depression, dizziness, urinary retention, somnolence, peripheral oedema, diarrhoea, headache and pruritus. Nausea or vomiting was treated with IV ondansetron 4 mg.

Patients were evaluated as outpatients for persistent pain at one and three months after surgery. The presence of pain was measured dichotomously (yes/no) and patients with pain were asked to rank its severity on a VAS scale. The Hospital Anxiety and Depression Scale (a 14-item instrument with two subscales of seven items each, measuring anxiety and depression over the past week) was administered.

In a retrospective analysis of eight hysterectomy patients, we observed a mean VAS pain score at three months of 2±1. Thus, 39 patients per group were expected to provide 80% power to detect a 30% reduction in pain score, at an alpha of 0.05. Demographic data were summarised using means and standard deviations and compared for balance by Student’s t-test or Pearson’s chi-square test, as appropriate. Non-parametric data were analysed with the Holm–Bonferroni–corrected Wilcoxon test. Pain scores were analysed using repeated measures of analysis of variance. A significance criterion of $P < 0.05$ was used. JMP Pro 9.0.00 (SAS Institute, Cary, NC, USA) software was used for statistical analysis.

RESULTS

Eighty-four patients were assessed for the study, and four patients declined participation. All 80 remaining patients were randomised and no patient data were excluded. The study duration, including to completion of follow-up, was two years, from January 2010 to January 2012.

There were no significant differences between the groups with respect to age, weight, height and American Society of Anesthesiologists physical status. Patients in the sevoflurane group had a longer duration of anaesthesia and surgical time (Table 1). Persistent surgical pain was less common and of lower intensity at both one and three months in the propofol group (Figures 1 and 2). Pain scores at rest or with movement were significantly higher in the sevoflurane group in the first four hours after surgery, with no significant difference at other time-points (Figures 3 and 4). Pethidine consumption did not significantly differ between groups. There were no significant differences in heart rate, oxygen saturation, mean blood pressure, respiratory rate, adverse events or sedation (data not reported). There were no significant differences between the groups with respect to anxiety and depression scores at one month, but scores were significantly lower in the propofol group at three months (Figures 5 and 6).

DISCUSSION

In this study, patients having open abdominal hysterectomy who were anaesthetised with propofol alone had a lower incidence and magnitude of persistent surgical pain and less early postoperative pain than those anaesthetised with propofol and sevoflurane.

There are conflicting findings in relation to the effect of propofol-based anaesthesia on acute postoperative pain. A number of previous clinical trials found that patients anaesthetised with propofol had less pain than patients maintained with isoflurane or sevoflurane. On the other hand, Fassoulaki et al reported that postoperative morphine consumption and pain did not significantly differ among groups of patients undergoing gynaecological procedures under sevoflurane, desflurane or propofol anaesthesia. Furthermore, in a study of patients having surgery for spondylolisthesis, randomised to propofol or sevoflurane, those in the sevoflurane group had lower pain scores compared to the propofol group. These differences might be due to investigation of different surgical populations, different pain management, random effects or unknown confounders.

Several mechanisms have been described to explain the effects of general anaesthetics on postoperative pain. Volatile anaesthetics seem to have a hyperalgesic effect which is mediated by central adrenergic and cholinergic transmission. Propofol demonstrates antinociceptive properties in different animal models, although there are conflicting results. Propofol has pronociceptive properties due to activation of transient receptor potential ion channels, but has...
analgesic characteristics at sedative doses\(^2\). Propofol also has direct effects on the dorsal horn neurons of the spinal cord, which play a significant role in the transmission of sensory information in a rat model\(^2\). In this study, pain scores in the early postoperative period were lower in the propofol group, which is consistent with the evidence from animal studies that propofol has antinociceptive and sevoflurane hyperalgesic properties.

Persistent surgical pain after hysterectomy is a common problem. The incidence determined in our study is higher than previously reported in the literature, possibly because of the face-to-face follow-up and testing. Our findings with respect to the lower incidence and intensity of persistent pain after hysterectomy are similar to those of the only other similar study to investigate persistent pain, which found a significant decrease after thoracotomy with propofol anaesthesia\(^1\). There are many possible explanations. First, better control of acute pain appears to decrease the incidence of persistent pain, and this was observed in our propofol group. Second, inflammation plays an important role in chronic pain, and propofol modulates inflammatory mediators, decreasing some\(^27,28\). Third, activation of microglia has been associated with chronic pain development, and propofol modulates microglial cellular responses\(^29,30\).

A secondary outcome finding in our study was that of better anxiety and depression scores three months after propofol anaesthesia. Although the difference in pain intensity was small and pain scores low among those patients with persistent pain, we speculate that this finding was a consequence of the higher incidence of persistent pain rather than a long-term effect of either propofol or sevoflurane, or a chance finding. Chronic pain has variable emotional and affective consequences, and these exploratory findings suggest phenotypical presentations of genetic influences that need to be addressed in future studies.

This study had several limitations. One is that postoperative pain is affected by a variety of factors other than the anaesthetic regimen, including the extent of the surgical procedure and genetic differences in response to analgesics and pain expression. In addition, we didn’t assess Hospital Anxiety and Depression Scale scores before surgery, so an imbalance between groups could explain our findings, although there is no apparent reason for such a difference other than chance. Future positive studies with a larger sample size will reduce the risk that our findings represent an alpha error. Of note is that sample size calculations in our study were based on historical data, and greater variability in our sample resulted in the study being underpowered for some outcomes.

In conclusion, our study demonstrated that general anaesthesia using propofol alone was associated with reduced early acute postoperative and persistent pain, compared to that after sevoflurane-based anaesthesia maintenance, in patients undergoing open hysterectomy. Although statistically significant, the clinical importance is limited by the small differences in the intensity of the pain. Future studies with larger sample sizes are needed in different chronic and acute pain settings.

REFERENCES


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