G. Boccara MD,
C. Mann MD,
Y. Pouzeratte MD,
A. Bellavoir MD,*
A. Rouvier MD,†
P. Colson MD

Improved postoperative analgesia with isoflurane than with propofol anaesthesia

Purpose: The impact of hypnotic drugs on postoperative analgesia has not been evaluated. We compared the influence of the maintenance of anaesthesia with either propofol or isoflurane on postoperative pain.

Methods: Forty ASA 1-2 women, undergoing cosmetic abdominoplasty were randomized to receive either 6-12 mg·kg⁻¹·hr⁻¹ propofol iv (P, n = 20) or MAC 1-1.5 isoflurane inhalation (Iso, n = 20). The lungs were ventilated with N₂O 60% and O₂ 40%, and 1 µg·kg⁻¹ fentanyl iv provided intraoperative analgesia. Before surgical closure, 2 g propacetamol iv were administered. Postoperative analgesia was provided after hourly assessment of pain (VAS 0-100 mm), with 10 mg nalbuphine iv if VAS ≥ 50 mm, during the eight hours after surgery. Sedation score (awake 0 to unrousable 4) was also recorded. Analgesia satisfaction score (nil 0 to excellent 4) obtained from the patient on discharge.

Results: Sedation scores were similar in both groups except in the first postoperative hour, when it was higher in the Iso group. The VAS at rest (15.4 ± 18.6 vs 29.7 ± 19.8 mm, $P = 0.0001$) and nalbuphine requirements (0.13 ± 0.35 vs 0.70 ± 0.80 doses, $P = 0.004$) were lower in the Iso group during the first six hours, although emesis was more frequent than in P (60 vs 25%; $P = 0.03$). The incidence of analgesia satisfaction score (≥3) was similar between the two groups (P: 95; Iso: 75%).

Conclusion: These results suggested that isoflurane anaesthesia provides better analgesia than propofol anaesthesia in the first six hours after abdominoplasty.

Objectif : Afin d'évaluer l'influence, sur l'analgésie postopératoire, des agents hypnotiques utilisés en anesthésie générale, nous avons comparé le propofol et l'isoflurane.

Méthodes : Quarante patientes ASA 1-2, devant subir une chirurgie esthétique de la paroi abdominale, ont reçu aléatoirement soit du propofol à 6-12 mg·kg⁻¹·hr⁻¹ (P, n = 20), soit de l'isoflurane à MAC 1-1,5 (Iso, n = 20). Sous N₂O 60 %, l'analgésie peropératoire était obtenue par du fentanyl iv 1 µg·kg⁻¹. Avant la fermeture chirurgicale, 2 g de propacétamol iv étaient administrés. La douleur postopératoire, évaluée toutes les heures pendant huit heures, par une échelle visuelle analogique (EVA 0-100 mm), était traitée par 10 mg de nalbuphine iv si EVA ≥ 50 mm. Un score de sédation (éveillé 0 à comateux 4) était noté durant 8 heures. Un score de satisfaction du patient concernant l'analgésie était recueilli à sa sortie de l'hôpital (nul 0 à excellent 4).

Résultats : Les scores de sédation étaient similaires dans les deux groupes, à l'exception d'une valeur plus élevée dans le groupe Iso lors de la première heure postopératoire. Les scores EVA au repos (15,4 ± 18,6 vs 29,7 ± 19,8 mm ; $P = 0,0001$) et la consommation de nalbuphine (0,13 ± 0,35 vs 0,70 ± 0,80 doses ; $P = 0,004$) étaient plus faibles que dans le groupe Iso pendant les six premières heures, malgré des épisodes de nausées et de vomissements plus fréquents que dans le groupe P (60 vs 25 % ; $P = 0,03$). L'incidence des scores élevés (3) de satisfaction des patients était comparable (P : 95 % ; Iso : 75 %).

Conclusion : Ces résultats suggèrent que l'isoflurane, en comparaison avec le propofol, procure une meilleure analgésie pendant les six premières heures postopératoires d'une abdominoplastie.

From the Department of Anaesthesiology and Intensive Care Medicine, DAR-B, Hôpital Saint-Eloi, Montpellier, France, and the Department of Plastic Surgery* and Department of Anaesthesiology,† Hôpital d'Instruction des Armées Bégin, St Mandé, France.

Address correspondence to: Dr Gilles Boccara, Département d'Anesthésie et de Réanimation B, Hôpital Saint-Eloi, 34295 Montpellier Cédex 5, France. Phone: 33-4-67-33-72-71; Fax: 33-4-67-52-48-06

Accepted for publication June 17, 1998.

HYPNOTIC drugs that are used to produce unconsciousness during general anaesthesia have little or no analgesic effect. General anaesthesia requires opioids to provide adequate analgesia during surgery. In animals, inhaled and intravenous agents inhibit nociceptive spinal transmission.¹⁻⁴ Using the rat paw formalin test, O'Connor *et al.* showed that isoflurane (1 MAC) and propofol (10 mg·kg⁻¹ *iv*) reduced spinal sensitization, although thiopentone had no effect and nitrous oxide antagonized the suppression of sensitization caused by isoflurane.⁴ However, as propofol is one of the most widely used hypnotics in anaesthesia, it is important to clarify its influence on nociception in clinical practice, particularly with regard to postoperative pain.

The aim of this study was to evaluate and compare the influence of two general anaesthesia techniques used for maintenance of anaesthesia, intravenous infusion of propofol or inhalation of isoflurane, on the intensity of postoperative pain.

Methods

The study was approved by the institutional ethical committee and each patient gave informed consent. We studied 40 women, ASA 1-2, scheduled to undergo cosmetic abdominoplasty surgery. The study design was prospective, randomized and blinded for the postoperative evaluation regarding anaesthetic agent.

During the preanaesthesia work-up, each patient was informed of the pain visual analog scale (VAS) consisting of a 100 mm line with 0 equal to "no pain" and 100 the "worst possible pain". Each patient received premedication with 0.5 mg alprazolam and 50 mg hydroxyzine *po*, one hour before induction of anaesthesia. After 250 ml lactated Ringer's solution, anaesthesia was induced in standardized form, with 3 mg·kg⁻¹ propofol, 3 µg·kg⁻¹ fentanyl and 0.6 mg·kg⁻¹ atracurium was used to facilitate tracheal intubation. Mechanical ventilation with N₂O 60% and O₂ 40% was adjusted to maintain P_{ET}CO₂ of 30-35 mmHg. Peroperative analgesia was maintained with 1 µg·kg⁻¹ fentanyl *iv* bolus as need, i.e. 20% increase in heart rate (HR) or mean arterial pressure (MAP) or lacrimation, and constant 60% end-expired nitrous oxide in oxygen. Maintenance of anaesthesia, after patient randomization, was with either 6-12 mg·kg⁻¹·hr⁻¹ propofol *iv* infusion (Group P, n = 20) or inhalation of isoflurane at 0.6-1% end-tidal concentration corresponding to 1-1.5 MAC isoflurane (Group ISO, n = 20) and adjusted to obtain a MAP > 60 mmHg, and < 85 mmHg. Crystalloid was infused at 5 ml·kg⁻¹·hr⁻¹.

The protocol for postoperative analgesia was standardized in both groups. Two grams propacetamol *iv*

were administered over 10 min, 30 min before surgical closure and repeated every six or eight hours. If propacetamol was ineffective, postoperative pain, defined by patient complaint or VAS > 50 mm, was treated, in both two groups, with 10 mg nalbuphine *iv* and repeated every hour if necessary. Pain and analgesia in the postoperative period were assessed 1) VAS was noted every hour at rest during eight hours postoperatively, 2) nalbuphine requirement in the eight hours after arrival in the postanesthesia care unit (PACU) and 3) patient satisfaction score for postoperative analgesia declared on discharge from hospital as follows: nil (0), mild (1), moderate (2), good (3), excellent (4). To evaluate residual anaesthesia in the postoperative period, sedation rate scores (wide awake = 0, mildly sleepy and response to verbal command = 1, moderately sleepy = 2, extremely sleepy = 3, unrousable to nociceptive stimulation = 4) were noted every hour for eight hours following arrival in the PACU.

Student's *t* test was used to compare intergroup data for age, weight, duration of surgery. The total amount of intraoperative fentanyl and of postoperative nalbuphine consumed were analyzed using the Mann-Whitney U-test. Data were expressed as means ± SD. Pain scores (VAS) and sedation scores were analyzed using two-way repeated-measures analysis of variance using the group as the independent sample factor and time after surgery as the repeated-measurement factor. They were expressed as mean values with 95% confidence interval. Comparison of the occurrence of side effects was made by Fisher's exact test. Differences were considered statistically significant if *P* ≤ 0.05.

Results

Demographic characteristics, surgical duration and peroperative fentanyl consumption were similar in the two groups (Table). Patients were awake and their tracheas were extubated on arrival in the PACU and it was possible to determine VAS. Sedation rating scores, similar in both groups at arrival in PACU (≥2), were higher in isoflurane than propofol group during the first hour, but no differences were found from the second to eighth postoperative hours (Figure 1).

The VAS scores at rest were lower in the isoflurane than in the propofol group from the first to the sixth hour after arrival in the PACU (Iso: 15.4 ± 18.6, P: 29.7 ± 19.8 mm; *P* = 0.0001) (Figure 2). Nalbuphine requirements (*P* = 0.004) and the number of patients requiring nalbuphine (*P* = 0.02) were lower in the isoflurane group. The percentage of patients expressing high satisfaction scores (3-4) was 75% and 95% in the propofol and isoflurane groups respectively, (*P*NS). The incidence of nausea in the eight hours after surgery was lower in the propofol group, i.e. 25%

FIGURE 1 Sedation scores (from 0 for wide awake to 4 for unrousable) between propofol (P) and isoflurane (ISO) for eight hours. Mean values with 95% confidence interval. * $P < 0.05$.

FIGURE 2 Assessment of postoperative analgesia using visual analog scale (VAS), during the eight hours after surgery. VAS 0 mm corresponded to "no pain", and 100 mm to worst possible pain. Mean values with 95% confidence interval. * $P < 0.05$.

vs 60% in the isoflurane group ($P = 0.03$) (Table). Three patients in the isoflurane group experienced vomiting, requiring treatment (metoclopramide) compared with none in the propofol group. None of the three patients required nalbuphine.

Discussion

Our results suggest that the use of isoflurane during general anaesthesia provides better analgesia than propofol in the first six hours after surgery. Otherwise, except for the first postoperative hour during which

TABLE Demographic data and perioperative characteristics according to each group.

	Propofol group (n = 20)	Isoflurane group (n = 20)
age (yr)	37.8 ± 9.7	40.2 ± 10.0
weight (kg)	57.4 ± 8.0	60.2 ± 9.5
surgery time (min)	115 ± 28	110 ± 27
total consumption of fentanyl (µg)	292.8 ± 67.0	288.9 ± 65.0
consumption of nalbuphine (dose)	0.70 ± 0.80	0.13 ± 0.35*
patients requiring nalbuphine in postoperative period (n/%)	10 (50%)	3 (15%)*
patients with nausea in eight hours postoperative period (n/%)	5 (25%)	12 (60%)*
patients' satisfaction regarding their analgesia, scores 3-4 (n/%)	15 (75%)	19 (95%)

Values are expressed as mean ± SD or number (%total).

* $P < 0.05$ between groups.

wake up was more rapid after propofol, alertness, assessed with sedation score, was similar in the two groups. Compared with isoflurane, propofol provides faster and more comfortable recovery of consciousness with fewer episodes of postoperative nausea and vomiting.⁵⁻⁷ As expected, nausea and vomiting were more frequent after isoflurane than after propofol. It should be noted that such vomiting can increase pain after parietal abdominal surgery. In addition, the quality of postoperative analgesia with isoflurane anaesthesia seemed much more intense that it was not reduced by the abdominal pain caused by nausea-vomiting.

The explanation for our results could be related to the pharmacokinetic differences between propofol infusion and isoflurane inhalation. First, we can speculate about the residual sedation and persisting plasma concentration in the early postoperative hours. Beyond this, in both groups, subanaesthetic concentrations were not measured. Furthermore, a combination of residual anaesthetic agent, opioid and propacetamol could be responsible for the sedation at one hour. Thus, in the isoflurane group, a hypnotic effect was noted in the first hour. In healthy volunteers submitted to experimental pain, propofol demonstrated an analgesic action at sub-hypnotic doses (0.25 to 0.5 mg·kg⁻¹ followed by 25 to 50 µg·kg⁻¹·min⁻¹).^{8,9} In clinical practice due to rapid elimination of propofol, postoperative measurements are generally much less. On the other hand, isoflurane at 0.10-0.20% had no analgesic action.^{10,11} We can, therefore, exclude the possibility that low residual quantities of these two agents could influence postoperative analgesia. Secondly, isoflurane, despite its low hepatic metabolism (0.17%), could reduce the hepatic biotrans-

formation of fentanyl or paracetamol. Moreover, paracetamol and fentanyl interactions are not established.

Several experimental studies have suggested that the choice of hypnotic agent could have a major effect on the development of postoperative pain. In a formalin test in rat, both 10 mg·kg⁻¹ propofol *iv* and isoflurane 1.4% reduced spinal sensitization.^{4,12} The results obtained with isoflurane were not improved when the concentration was increased whereas lower concentrations nullified its effects.^{1,12} Petersen-Felix *et al.* showed that propofol, in subhypnotic doses (10 µg·kg⁻¹·min⁻¹ and 30 µg·kg⁻¹·min⁻¹), had no analgesic effect to electrical and heat stimulation, but had a hyperalgesic effect to mechanical pressure pain in healthy volunteers.¹³ Also, the possibility that either isoflurane has an analgesic effect or propofol has a hyperalgesic effect, could be proposed as a pharmacodynamic explanation.

The association of morphine with isoflurane markedly improves spinal inhibition¹ but the effects of the association of propofol-morphine are unknown. Following our results, we hypothesise that the association of isoflurane-fentanyl could have more marked potentiating effects than the association of propofol-fentanyl on the blockage of spinal sensitivity measured by the level of postoperative pain. Moreover, nitrous oxide may have an antagonistic effect on the suppression of spinal sensitization by other general anaesthetics such as halothane,⁴ but this has not been reported in combination with isoflurane or propofol. Further clinical and experimental studies should be performed in order to establish such interactions.

In conclusion, anaesthesia by isoflurane inhalation improves early postoperative analgesia after abdominoplasty compared with anaesthesia by continuous propofol infusion.

References

- 1 Abram SE, Yaksh TL. Morphine, but not inhalation anesthesia, blocks post-injury facilitation. The role of preemptive suppression of afferent transmission. *Anesthesiology* 1993; 78: 713–21.
- 2 Jewett BA, Gibbs LM, Tarasiuk A, Kendig JJ. Propofol and barbiturate depression of spinal nociceptive neurotransmission. *Anesthesiology* 1992; 77: 1148–54.
- 3 Namiki A, Collins JG, Kitahata LM, Kikuchi H, Homma E, Thalhammer JG. Effects of halothane on spinal neuronal responses to graded noxious heat stimulation in the cat. *Anesthesiology* 1980; 53: 475–80.
- 4 O'Connor TC, Abram SE. Inhibition of nociception-induced spinal sensitization by anesthetic agents. *Anesthesiology* 1995; 82: 259–66.
- 5 Doze VA, Shafer A, White PF. Propofol-nitrous oxide versus thiopental-isoflurane-nitrous oxide for general anesthesia. *Anesthesiology* 1988; 69: 63–71.
- 6 Korttila K, Östman P, Faure E, *et al.* Randomized comparison of recovery after propofol-nitrous oxide versus thiopentone-isoflurane-nitrous oxide anaesthesia in patients undergoing ambulatory surgery. *Acta Anaesthesiol Scand* 1990; 34: 400–3.
- 7 Valanne J. Recovery and discharge of patients after long propofol infusion vs isoflurane anaesthesia for ambulatory surgery. *Acta Anaesthesiol Scand* 1992; 36: 530–3.
- 8 Anker-Møller E, Spangsbørg N, Arendt-Nielsen L, Schultz P, Kristensen MS, Bjerring P. Subhypnotic doses of thiopentone and propofol cause analgesia to experimentally induced acute pain. *Br J Anaesth* 1991; 66: 185–8.
- 9 Zacny JP, Coalson DW, Young CJ, *et al.* Propofol at conscious sedation doses produces mild analgesia to cold pressor-induced pain in healthy volunteers. *J Clin Anesth* 1996; 8: 469–74.
- 10 Petersen-Felix S, Arendt-Nielsen L, Bak P, *et al.* Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by experimentally induced pain. *Br J Anaesth* 1995; 75: 55–60.
- 11 Tomi K, Mashimo T, Tashiro C, *et al.* Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *Br J Anaesth* 1993; 70: 684–6.
- 12 Goto T, Marota JJA, Crosby G. Volatile anaesthetics antagonize nitrous oxide and morphine-induced analgesia in the rat. *Br J Anaesth* 1996; 76: 702–6.
- 13 Petersen-Felix S, Arendt-Nielsen L, Bak P, Fischer M, Zbinden AM. Psychophysical and electrophysiological responses to experimental pain may be influenced by sedation: comparison of the effects of a hypnotic (propofol) and an analgesic (alfentanil). *Br J Anaesth* 1996; 77: 165–71.