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Randomized evaluation of ketorolac vs. fentanyl in elderly patients undergoing ambulatory surgery

L. Targa [a,*], L. Droghetti [a], M. Terenzoni [b], A. Chieregato [a], M. Simone [c], F. Zucchi [d], M.E. Forini [e], R. Zatelli [a]

[a] *1st Department of Anaesthesia and Intensive Care, Azienda Ospedaliera S. Anna, Corso Giovecca, 203, 44100 Ferrara, Italy*
[b] *Department of Anaesthesia and Intensive Care, University of Ferrara, Ferrara, Italy*
[c] *Department of Urology, Azienda Ospedaliera S. Anna, Ferrara, Italy*
[d] *Department of Radiology, Azienda Ospedaliera S. Anna, Ferrara, Italy*
[e] *Biostatistical, University of Ferrara, Ferrara, Italy*

Abstract

Analgesic efficacy of a preemptive single dose preemptively of Ketorolac or Fentanyl in 102 elderly men undergoing general anaesthesia for multiple prostatic biopsies was assessed. Patients were randomly allocated to receive either (group A) Ketorolac 0.55 mg/kg intravenously (IV) 15 min before surgery or (group B) fentanyl 1, μg/kg IV 5 min before surgery. Anaesthesia was induced by means of propofol 15 mg/kg per h and maintained by means of propofol 7 mg/kg per h while patients were ventilated spontaneously using N_2O 70% in O2 via a to and fro system. Routine monitoring included mean arterial pressure (MAP), heart rate (HR), pulse oxygen saturation (SpO_2), respiratory rate (RR), end tidal CO_2 ($EtCO_2$). HR and MAP decreased during surgery with significantly lower values in the Fentanyl group. Fentanyl treated patients had higher ventilatory depression with frequent intraoperative apnoea. Group A needed supplemental doses of propofol to maintain adequate sedation. Sixty and 120 min postanaesthesia no differences were found for MAP, HR, RR, $EtCO_2$, pain and the tolerability of the procedure. The Ketorolac group had less adverse effects and could be discharged earlier © 1997 Elsevier Science Ireland Ltd.

Keywords: Elderly outpatients; Fentanyl; Ketorolac tromethamine; Prostatic biopsy; Day surgery; Pain; Drug cost

1. Introduction

For social and economic reasons outpatient procedures continue to increase in popularity. Elderly patients, more than others, can be involved in unexpected hospital admission for either surgical or anaesthetic sequelae [1–6].

In these patients the anaesthesiologist is required to provide safe analgesia, proper operating conditions and ensure rapid recovery with minimal postoperative sequelae assuring proper respect for discharge criteria. The potent and rapid acting opioid Fentanyl, despite many well known side effects, provides good intraoperative conditions and effective pain relief on emergence from general anaesthesia. [7,8].

Ketorolac tromethamine is a non-steroidal anti-inflammatory drug, available in parenteral as well as oral form, which has negligible effects on ventilatory control, hemodynamics and psychomotor control [9–12].

The aim of this study is to evaluate the impact of a minor analgesic like Ketorolac on intra and postoperative analgesia and discharge criteria compared to a major analgesic like Fentanyl, as part of a balanced anaesthesia with Propofol and N_2O in elderly patients undergoing prostatic ultrasound guided biopsies of the prostate.

2. Patients and methods

After obtaining institutional review board approval and written informed consent, 102 elderly men sched-

* Corresponding author. Fax: + 39 532 209998.

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Table 1
Demographic characteristics

	A ($n = 51$)	B ($n = 51$)	t-test
Age (years)	65.7 ± 6.6	63.7 ± 5.8	N.S
Weight (kg)	75.6 ± 9.5	78.3 ± 12.2	N.S
Height (cm)	171.7 ± 6.2	173.2 ± 5.9	N.S
BSA (m^2)	1.88 ± 0.14	1.92 ± 0.14	N.S

Mean values ± D.S. Group A = Ketorolac. Group B = Fentanyl.

uled for multiple prostatic biopsies (ultrasound guided) were enrolled in this study.

Patients, who were graded ASA physical status 1 or 2, with a median age of 64.7 ± 6.25, and satisfied the inclusion criteria, received IM atropine 0.01 mg/kg as premedication 30 min before coming to the operating room.

On arrival at the operating room, routine monitoring was applied, including ECG, non invasive automatic blood pressure cuff, pulse oximeter (SpO_2), end-tidal CO_2 ($EtCO_2$) and respiratory rate.

Patients were randomly allocated to two equal groups, to receive either Ketorolac 0.55 mg/kg (Group A, $n = 51$) or Fentanyl 1 μg/kg IV. (Group B, $n = 51$) respectively 15 and 5 min prior to the induction of anaesthesia, after placement of an IV catheter.

Anaesthesia was induced with Propofol 15 mg/kg per h and patients were allowed to breath spontaneously a mixture 70% nitrous oxide in oxygen via a to and fro system. The ultrasound examination was then performed using a transrectal biplanar-linear 7.5 MHz probe and a 14 ch, 20 cm long needle was inserted in the perineum. In the absence of signs of inadequate anaesthesia, Propofol was infused at 7 mg/kg per h.

Before induction (TO), 5, 10, 15 min after induction (T5, T10, T15) and 60, 120 min (T60, T120) after the end of Propofol infusion, mean arterial blood pressure (MAP), heart rate (HR), respiratory rate (RR), SpO_2 and end tidal CO_2 ($EtCO_2$) were recorded.

After discontinuation of Propofol and nitrous oxide we recorded when the patient spontaneously opened his eyes (time to eye opening), responded to simple verbal command to squeeze the investigator's hand (time to following commands), and gave their correct date of birth.

At 60 and 120 min after emergence we used a pain intensity score PIS (O = no pain, 1 = mild, 2 = moderate, 3 = severe) to assess pain and a visual analogue scale VAS (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent) to assess the tollerability of the procedure. The requirements of incremental doses of anaesthetics and postoperative side effects were noted.

Six to eight prostatic biopsies were taken with the patients in the lithotomy position. Throughout the procedure 10 ml/kg normal saline was infused.

Surgical and ultrasonographic procedures were performed by the same physicians; even anaesthesia was administered by one anaesthetist who was aware of the analgesic agent used, but who took no part in the assessments. Monitoring data and recovery were recorded by a second anaesthesiologist unaware, in turn, of the anaesthetic technique used.

The amount of drugs administered intravenously was noted and cost analysis was performed.

3. Data and statistical analysis

3.1. Data transformation

All routine monitoring parameters at $T_n(T_5–T_{120})$, were computed as their per cent difference from TO, considered as baseline value, according to the formula: (TO − Tn):TO × 100.

Table 2
HR, MAP, RR, $EtCO_2$, SpO_2, during surgery

Times	Mean values (S.D)						Friedman test	
	Group A ($n = 51$)			Group B ($n = 51$)			A and B	T5-T10-T15
	T5	T10	T15	T5	T10	T15		
R	0.68 (10.9)	2.16 (12.31)	4.37 (12.11)	4.64 (12.22)	10.5 (15.3)	11.9 (14.2)	***	***
MAP	6.67 (9.8)	12.22 (11.31)	16.46 (10.53)	10.3 (8.9)	17.2 (9.13)	19.6 (9.9)	*	***
RR	−3.92 (25.6)	−10.83 (25.6)	−14.96 (24.58)	27.5 (41.3)	31.14 (47.1)	15.23 (39.32)	***	***
$EtCO_2$	−5.1 (13.5)	−3.53 (16.2)	−4.09 (16.03)	−7.5 (13.4)	−15.25 (18.3)	−16.95 (19.7)	***	N.S.
SPO_2	0.09 (1.8)	013 (1.7)	−0.31 (1.54)	0.45 (2.75)	1.25 (3.54)	0.84 (2.17)	N.S	N.S

T5, T10,T15, are recorded as their percent differences from T0, considered as baseline value according to the formula: (T0 − Tn): T0 × 100.
Statistical analysis among times and between groups.Group A = Ketorolac. Group B = Fentanyl
* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$

Table 3
HR, MAP, RR, $EtCO_2$, SpO_2, during recovery

Times	Group A ($n = 51$)		Group B ($n = 51$)		Test	
	T60	T120	T60	T120	Gruppi	Tempi
$EtCO_2$	1.34 (7.94)	2.0 (8.17)	−0.6 (10.6)	−1.82 (10.4)	N.S[a]	N.S[a]
RR	−0.34 (17.3)	3.12 (19.7)	0.39 (31.3)	4.06 (23.89)	N.S[b]	N.S[b]
HR	9.19 (13.8)	10.83 (14.8)	10.63 (18.32)	12.03 (17.61)	N.S[a]	N.S[a]
MAP	8.99 (11.8)	8.8 (11.29)	8.95 (11.4)	7.78 (10.25)	N.S[a]	N.S[a]
SPO_2	−0.01 (1.27)	0.01 (1.25)	0.06 (1.56)	1.32 (8.27)	N.S[b]	N.S[b]

Mean Values (S.D) of T60 and T120 from discontinuation of N_2O and propofol.
Statistical analysis among times and between groups T60 and T120 are recorded as their diferences from To, considered as baseline value according to the formula (T0 − Tn):T0 × 100.
Group A = Ketorolac. Group B = Fentanyl.
[a] Two-ways ANOVA
[b] Friedman test

3.2. Statistical analysis:

To verify the effects of the analgesics on per cent variations at T5, T10, T15, T60, T120 with respect to TO, the Friedman Test was used when it was impossible to show that the data were normally distributed, and two-ways ANOVA when it was possible [13,14].

The Mann–Whitney test was used to analyze differences in recovery, induction and total times between the two groups.

PIS data, expressed as frequency, in two groups at T60 and T120 were examined using the Fisher test.

In all cases a P error, less than 0.05 in rejecting H_0 hypothesis, was considered a statistically significant result thus defining a threshold at $P = 0.05$.

4. Results

Table 1 shows that there was no significant difference between the demographic characteristics of the two groups.

Table 2 and Table 3 show mean values and standard deviation (S.D.) of per cent differences at T5, T10, T15, T60, and T120 with respect to TO of HR, MAP, RR, $EtC0_2$, SpO_2. Both HR and MAP decrease in both groups at time 5, 10 and 15 with significantly lower values in the Fentanyl group; even the differences between time were significant while no difference was found at T60 and T120. There was no statistical difference in SpO_2 recorded in both groups. However, in the Fentanyl group frequent episodes of apnoea, followed by immediate assisted ventilation, could have influenced these data.

At T5, T10 and T15, RR increased in Group A, but decreased in Group B, with significant differences between both groups and times, while at T60 and T120 no differences were noted.

Table 4 shows that in Group A both induction and total anaesthesia times were significantly longer.

There were no differences between groups either for PIS or for VAS (Fig. 1, Fig. 2). Awakening time determined from discontinuation of Propofol and N2O, was considered the time when the patients could open their eyes, respond to verbal command and demonstrate orientation in time and space giving their correct date of birth. There were no differences between groups as to awakening time, but time to following commands proved to be near the threshold (Table 5).

Ketorolac, administered before surgery, had less intraoperative and postoperative side effects than Fentanyl (Table 6).

Analysis of intravenous anaesthesia drugs revealed a higher cost in the Ketorolac Group, but we did not take into account other anaesthesia-related direct and indirect costs, such as inhalatory drugs, staff time, equipment and supplies (Table 7).

Table 4
Induction time (T1), Surgery time (T2) and total anaesthesia time (T3)

	A ($n = 51$)	B ($n = 51$)	Mann Whitney test
T1 (min)	7 ± 2.6	6.08 ± 2.69	**
T2 (min)	10 ± 4.44	7.98 ± 3.85	*
T3 (min)	17 ± 4.27	14.06 ± 3.97	***

Mean Values ± S.D. and statistical analysis.
Group A = Ketorolac. Group B = Fentanyl.
* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$

5. Discussion

In elderly patients anaesthetics have to provide intraoperative and postoperative analgesia, reduce metabolic

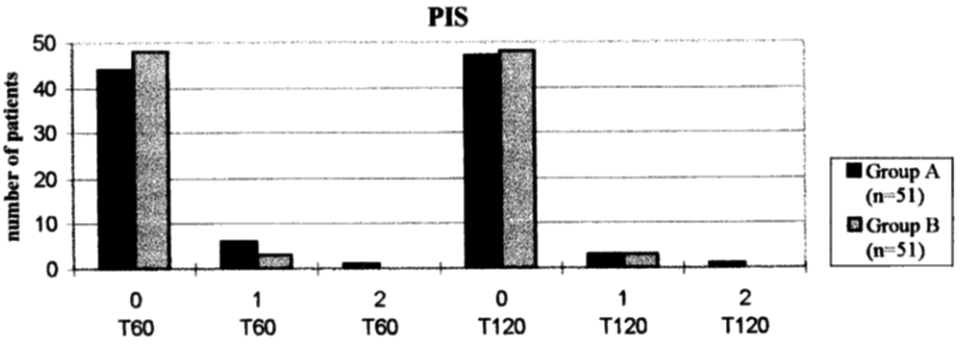

Fig. 1. Pain Intensive score (0–3) after 60 and 120 min. (T60–T120) from discontinuation of N_20 and Propofol. Score: 0 = no pain, 1 = mild, 2 = moderate, 3 = severe.

and autonomic responses to surgery, provide a rapid emergence from anaesthesia, low incidence of side effects and a short recovery time. Propofol, for its pharmacokinetics, compartment constants and clearance, seems to achieve this goal better than benzodiazepines and barbiturates [15–17].

The volume of central compartment and total body clearance is reduced more in the elderly than in adults and in children thereby reducing the dose required for induction and maintenance [4].

Dose and infusion rate influence the pharmacodynamic effects: a slow infusion, through a syringe pump, can be titrated to obtain satisfactory surgical conditions, minimizing adverse effects [3–6]. Nevertheless, hypotension, reduced cardiac output, ventilatory depression are more frequent when Propofol is associated with N_2O and/or to opioids [18].

Setting the induction rate at 15 mg/kg per h and the maintenance at 7 mg/kg per h, during surgery, a reduced MAP was more evident when Fentanyl was used, even though at low dose (1 μg/kg). MAP decreased less than 20% of the baseline value, partly due to the associated reduction in HR (Table 2). In fact clinical reports on Propofol describe slow heart rates despite a decrease in arterial pressure. Propofol causes resetting of the baroreflex without depressing its sensitivity, enabling a slower heart rate to be maintained despite any fall in blood pressure [19,20].

Diclofenac dosage (0.55 mg/kg IV) had to assure a plasma concentration appropriate for providing effective pain relief in a comparable group of patients undergoing suprapubic prostatectomy (Zatelli R. et al. unpublished data). We administered ketorolac 15 min before surgery in order to achieve plasma levels high enough to inhibit prostaglandine synthesis prior to tissue injury and to prevent central nociceptive sensation [9,21,22].

As Ketorolac has no cardiorespiratory depressant effect [11,12], the reduction in MAP and HR observed in the Ketorolac group could be related to Propofol, as well as the increase of $EtCO_2$ while spontaneous ventilation was maintained. On the other hand, Fentanyl treated patients had ventilatory depression, higher increase of $EtCO_2$, decreased RR up to frequent apnoea (Table 6).

Intraoperative requirements for supplemental Propofol and RR increase could suggest an occasionally inadequate analgesic effect produced by Ketorolac in this procedure (Table 2), while good PIS and VAS values and the significantly lower incidence of side effects indicated proper postoperative analgesia and comfort. Patients could be discharged 60 min after surgery (Table 6, Fig. 1 and Fig. 2).

Fentanyl enhanced Propofol's hypnotic action, providing a shorter induction and global time and a lower necessary dose of Propofol (Table 4). So the

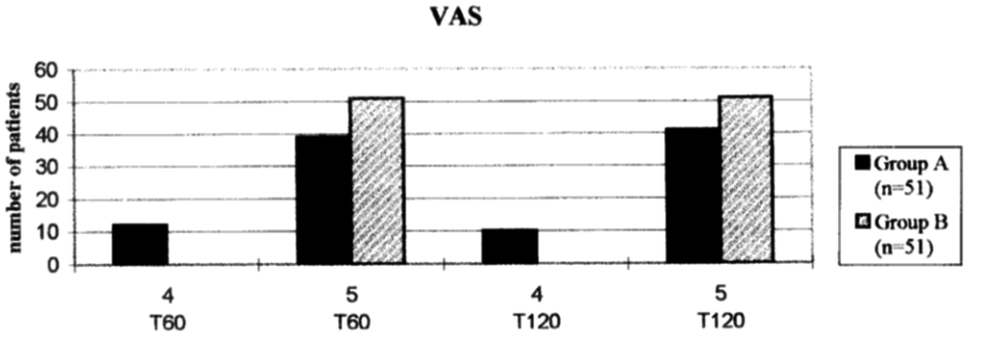

Fig. 2. Visual Analogic Scale (1–5) after 60 and 120 min. (T60–T120) from discontinuation of N_2O and Propofol. Score: 1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = exellent.

Table 5
Time to emerge from anaesthesia determind from discontinuation of N_2O and propofol

	Mean values S.D.		
	A ($n = 51$)	B($n = 51$)	Mann-Whitney test
Time to eye opening (min)	4.25 ± 1.41	3.9 ± 1.97	N.S
First response to verbal command (min)	5.14 ± 1.48	4.49 ± 1.99	N.S
Oriented to time, place (min)	5.88 ± 1.7	5.55 ± 2.26	N.S

Mean values ± S.D. and statistical analyisis.
Group A = Ketorolac. Group B = Fentanyl

shorter time to follow commands ($P < 0.06$) may be related to the lower dose of Propofol used in the Fentanyl group (Table 5). Mild nausea had the same incidence in the two groups and could be related to the position, manual ventilation via a facial mask and to N_2O [23,24], drowsiness and headache were more frequent in the Fentanyl group (Table 6) and could possibly have been prevented in these elderly patients with the use of short acting optioids (sufentanyl or alfentanyl) [25–27].

The cost of IV drugs was significantly higher with Ketorolac, both because the drug itself is more expensive than Fentanyl, and because a larger amount of Propofol was required (Table 4, Table 7). In summary, Ketorolac given intravenously in Propofol anaesthesia, being associated with less intraoperative and postoperative side effects, may offer some advantages over opioids. Though involving a higher anaesthesia drug cost, it could save PACU nursing time and costs and assure a shorter time to discharge the patient [28–30]. More comprehensive studies on cost analysis are still necessary.

Table 6
Intraoperative and postoperative side effects

	A ($n = 51$)	B ($n = 51$)
Intraoper. apnoea	—	16 (31%)
Nausea	2 (3.9%)	1 (1.9%)
Somnolence	—	3 (5.9%)
Headache	—	1 (1.9%)
Total	2 (3.9%)	21 (40.7%)

Rate and % in group A = Ketorolac and group B = Fentanyl.

Table 7
Anaesthesia drugs costs

Group	Means	S.D.
A ($n = 51$)	£ 5035.5	557.6
B ($n = 51$)	£ 1522.3	410.1

T-test, $P < 0.001$. £ (Italian coin).
Group A = Ketorolac. Group B = Fentanyl.

References

[1] Davies PRE, Ogg TW. Managing anaesthesia for geriatric day surgery. J One Day Surg 1993;2:16–18.
[2] Harper KW, Collier PS, Dundee JW. Age and nature of operation influence the pharmacokinetics of midazolam. Br J Anaesth 1985;57:866–71.
[3] Peacock JE, Lewis RP, Reilly CS, Nimmo S. Effect of different rates of infusion of propofol for induction of anaesthesia in elderly patients. Br J Anaesth 1990;65:346–352.
[4] Kirkpatrick T, Cockshott ID, Douglas EJ, Nimmo WS. The pharmacokinetics of propofol in elderly patients. Br J Anaesth 1988;60:146–50.
[5] Zatelli R, Marchi M, Fabbri E, Targa L, et al. La gestione perioperatoria del paziente anziano. Minerva Anestesiologica 1994;60 Suppl 9:17–24.
[6] Thompson EM, Mathews HM, McAuley DM. Problems in day care surgery. Ulster Med J 1991;60(2):176.
[7] Horrigan RW, Moyers JR, Johnson BH, Egger EI II, Margolis A, Goldsmith S. Etomidate vs. thiopental with and without fentanyl. A comparative study on awakening in man. Anesthesiology 1980;52:363–364.
[8] Rigg JR, Goldsmith CH. Recovery of ventilatory response to carbon dioxide after thiopentone morphine and fentanyl in man. Can Anaesth Soc J 1976;23:370–82.
[9] Rooks WH, Maloney PJ, Shott LD, Schuler ME et al. The analgesic and anti-inflammatory profile of Ketorolac and its Tromethamine salt. Drugs Exptl Clin Res 1985;XI(8):479–92.
[10] Hitchcock M, Ogg TW. Acute post-operative pain management in day case surgery patients In: Camu F, editor. Pain management. Chester: Adis International, 1994:1–15.
[11] Murray AW, Brockway MS, Kenny GNC. Comparison of the cardiorespiratory effects of Ketorolac and Alfentanil during propofol anaesthesia. Br J Anaesth 1989;63:601–3.
[12] Camu F, Van Overberge L, Bullingham R, Lloyd J. Hemodynamic effects of two intravenous doses of Ketorolac Tromethamine compared with morphine. Pharmacotherapy 1990;10(6 Suppl. 2):122S–126S.
[13] Peter Armitage. Statistical methods in medical research Blackwell, Oxford, 1971.
[14] Altman DG. Practical statistics for medical research, first ed. London: Chapman and Hall, 1991:456.
[15] Smith J, White PF, Nathanson M, Gouldson R. Propofol. An update on its clinical use. Anesthesiology 1994;81:1005–1043.
[16] Hughes MA, Glass PSA, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology 1992;76:334–41.
[17] Kashtan H, Edelist G, Mallon J, Kapala. Comparative evaluation of propofol and thiopentone for total intravenous anaesthesia. Can J Anaesth 1990;37(2):170–6.
[18] Coates DR, Monk CR, Prys-Roberts C, Turtle MJ. Hemodynamic responses of hypertensive patients to an infusion of

propofol to supplement nitrous oxide anaesthesia. Beitr Anaesthesiol Intensiv Med 1987;20:107–8.

[19] Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J. Effect of propofol on baroreflex activity in humans. Anesth Analg 1987;66:1115–20.

[20] Samain E, Marty J, Gauzit R et al. Effects of propofol on baroreflex control of hearth rate and on plasma noradrenaline levels. Eur J Anaesthesiol 1989;6:321–326.

[21] Woolf CJ, Chong MS. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77:362–379.

[22] Higgins MS, Givogre JL, Marco AP, Blumenthal PD, Furman WR. Recovery from outpatient laparoscopic tubal ligation is not improved by preoperative administration of ketorolac or ibuprefen, Anesth Analg 1994;79:274–80.

[23] Watcha MF, White PF. Postoperative nausea and vomiting. Anesthesiology 1992;77:162–84

[24] Felts JA, Poler SM, Spitznagel EL. Nitrous oxide, nausea and vomiting after outpatient gynecology surgery. J Clin Anesth 1990;2(3):168–71

[25] Steven L, Shafer M.D, John R, Varvel M. Pharmacokinetics, Pharmacodynamics, and rational oppioid selection. Anesthesiology 1991;74:53–63.

[26] Phitayacorn P, Melnick BM, Vicinie AF. Comparison of sufentanil and fentanyl infusions for outpatient anaesthesia. Can J Anaesth 1987;64:242–45

[27] White PF, Coe V, Shafer A, Sung ML. Comparison of alfentanil with fentanyl for outpatient anesthesia. Anesthesiology 1986;64:99–106

[28] Cade L, Morley PT, Ross AW. Is propofol cost-effective for day surgery? Anesth Intensive Care 1991;19(2):201–204

[29] Dexter F, Tinker JF. Analysis of strategies to decrease postanesthesia care unit costs. Anesthesiology 1995;82(1):94–101

[30] Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia vs. thiopental sodium-isoflurane-nitrous oxide anesthesia. J Clin Anesth 1991;3(5):391–394