Synergistic sedation with propofol and midazolam in intensive care patients after coronary artery bypass grafting

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Objectives: To evaluate and compare the clinical efficacy, impact on hemodynamics, safety profiles, and cost of combined administration of propofol and midazolam (synergistic sedation) vs. midazolam and propofol administered as sole agents, for sedation of mechanically ventilated patients after coronary artery bypass grafting.

Design: Prospective, controlled, randomized, double-blind clinical trial.

Setting: Intensive care unit of SCIAS-Hospital de Barcelona.

Patients: Seventy-five mechanically ventilated patients who underwent coronary artery bypass graft surgery under low-dose opioid anesthesia.

Interventions: According to the double-blind method, patients were randomly assigned to receive propofol (n = 25), midazolam (n = 25), or propofol combined with midazolam (n = 25). Infusion rates were adjusted to stay between 8 and 11 points on Glasgow Coma Score modified by Cook and Palma.

Measurements and Main Results: Mean ± SD duration of sedation was 14.4 ± 1.5 hrs, 14.1 ± 1.1 hrs, and 14.7 ± 1.9 hrs for the propofol, midazolam, and synergistic groups, respectively. The induction dose was 0.55 ± 0.05 mg/kg for propofol as sole agent, 0.05 ± 0.01 mg/kg for midazolam as sole agent, and 0.22 ± 0.03 mg/kg for propofol administered in combination with 0.02 ± 0.00 mg/kg of midazolam ($p = .001$). The maintenance dose was 1.20 ± 0.03 mg/kg/hr for propofol as sole agent, 0.08 ± 0.01 mg/kg/hr for midazolam as sole agent, and 0.50 ± 0.09 mg/kg/hr for propofol administered in combination with 0.03 ± 0.01 mg/kg/hr of midazolam ($p < .001$). All sedative regimens achieved similar efficacy in percentage of hours of adequate sedation (93% for propofol, 88% for midazolam, and 90% for the synergistic group, respectively). After induction, both propofol and midazolam groups had significant decreases in systolic blood pressure, diastolic blood pressure, left atrial pressure, and heart rate. Patients in the synergistic group had significant bradycardia throughout the study, without impairment in other hemodynamic parameters. Patients sedated with propofol or synergistic regimen awoke sooner and could be extubated before those patients sedated with midazolam (0.9 ± 0.3 hrs and 1.2 ± 0.6 hrs vs. 2.3 ± 0.8 hrs, respectively, $p = .01$). Synergistic sedation produced cost savings of 28% with respect to midazolam and 68% with respect to propofol.

Conclusions: In the study conditions, the new synergistic treatment with propofol and midazolam administered together is an effective and safe alternative for sedation, with some advantages over the conventional regimen with propofol or midazolam administered as sole agents, such as absence of hemodynamic impairment, >68% reduction in maintenance dose, and lower pharmaceutical cost. (Crit Care Med 1998; 26:844–851)

KEY WORDS: coronary artery bypass; hemodynamics; intensive care unit; mechanical ventilation; midazolam; pharmacoeconomics; postoperative care; propofol, synergistic sedation; weaning

Coronary artery bypass grafting is a common surgical procedure performed on 330,000 patients in the United States (1) in 1994. The majority of these patients required admission to the intensive care unit (ICU) for postoperative care, which included a short period of controlled mechanical ventilation. This supportive treatment is essential both for patient stabilization, and to facilitate the metabolism of high opiod doses and muscle relaxants administered during operative anesthesia (2). Under these circumstances, controlled sedation and adequate analgesia are often necessary to provide patient comfort, prevent patient-ventilator asynchrony, and facilitate specific procedures such as endotracheal suctioning. An additional benefit to postoperative sedation is the control of hypertension and tachycardia secondary to agitation, which has been related to postoperative myocardial ischemia after coronary artery graft surgery (3).

Since there is no ideal sedative agent available, researchers have evaluated a wide variety of drugs. Among the possible alternatives, both propofol and midazolam have proven useful for this indication. Most comparative studies between these drugs confirm both their efficacy and their safety as well as some disadvantages. Propofol is an alquilphenol with a high distribution

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volume and rapid elimination with few cumulative effects, which is increasingly used for short-term sedation in critically ill patients as well as for patients after cardiac surgery (4). Nevertheless, the induction of postoperative sedation with this agent can induce arterial hypotension (5). Midazolam is a benzodiazepine with a favorable pharmacokinetic profile due to shorter half-life, pH dependent solubility which facilitates continuous intravenous infusion, and shorter half-life of its active metabolites. However, in some critically ill patients, their pharmacokinetic properties can change, causing longer duration of action after discontinuation (6, 7).

To take advantage of the best characteristics of each agent, one possible strategy could be their combined administration. The combined use of propofol and midazolam acts synergistically for induction of operative anesthesia with a reduction of ~44% in required doses (8). For this reason, synergistic sedation is widely employed in the daily practice of anesthesiology. Otherwise, the efficacy and safety of this promising treatment in critically ill patients remains unknown.

We evaluated and compared propofol and midazolam as sole agents with their combined use in mechanically ventilated patients who required sedation after coronary artery bypass grafting. We tested a four-point hypothesis about synergistic sedation to evaluate: a) similar efficacy in terms of quality of sedation; b) better safety due to lower hemodynamic impact; c) fast recovery time, similar to propofol and faster than midazolam; and d) reduction in pharmaceutic cost due to lower required doses.

MATERIALS AND METHODS

The Ethics and Research Committee of our hospital approved this prospective, comparative, randomized, and double-blind study. We evaluated all adult patients, admitted to the SCIAS-Hospital de Barcelona between January 1994 and January 1996, for elective coronary artery bypass graft surgery. In all cases, informed consent was obtained from the patient. Inclusion criteria were: minimum age 16 yrs, probable need for controlled mechanical ventilation for a period of between 14 and 16 hrs, previous heart failure status valued as class I or II of the New York Heart Association, low anesthetic risk classified as class I or II of the American Society of Anesthesiologist (ASA) scale. Exclusion criteria were known or suspected allergy to propofol, midazolam, or other trial drugs, known or probable pregnancy, history of stroke, dementia or seizures, renal failure manifested by serum creatinine of >3.5 mg/dL (>309.4 μmol/L), liver failure manifested by serum total bilirubin of >5 mg/dL (>85.5 μmol/L), severe left ventricular dysfunction values such as ejection fraction <35% based on preoperative echocardiographic or angiographic assessment, hemodynamic instability defined as systolic blood pressure of <100 mm Hg at time of randomization, and gross obesity evaluated as a >20% increase in body mass index according to standard height/weight table. Eighty-three patients met the inclusion criteria, eight of whom were excluded according to the above-cited criteria (one due to presence of renal failure, five due to previous severe left ventricular dysfunction, and two due to hemodynamic instability).

The randomization process was done before initiating the study, according to a table of two-digit random numbers generated by computer.

Operative anesthesia consisted of a standardized regimen of fentanyl (<30 μg/kg), diazepam (<1 mg/kg), and isoflurane and pancuronium bromide for neuromuscular block. Neuromuscular block was not reversed at the end of the operation.

The study period began postoperatively when the patient was admitted to the ICU, and continued for 14 to 16 hrs during mechanical ventilation and weaning.

The sedation score was assessed on a continuous basis, according to the Glasgow Coma Score modified by Cook and Palma (GCSC) (9), which is based on the best reactivity response. This scale has scores ranging between 4 and 18 points (Table 1). Sedation was considered adequate if the degree of reactivity stayed between 8 and 11 points GCSC, insufficient if the score was ≥12 points GCSC, and excessive if the score was between 4 and 7 points GCSC.

After admission to the ICU, the 75 remaining patients received no sedation other than analgesic morphine infusion (0.015 mg/kg/hr) and additional bolus doses (0.015 mg/kg) during potentially painful procedures. When the sedation score was ≥12 points GCSC, patients were assigned randomly to receive, according to the double-blind method (blinding of nurses and physicians to the sedative medication the patient received), midazolam (n = 25), propofol (n = 25), or midazolam and propofol administered together (n = 25). Propofol (Diprivan®, 2,6-diisopropylphenol, Zeneca Farma SA, Porriño, Spain) as sole agent, was administered in 20-mL vials containing emulsion to a concentration of 10 mg/mL. A placebo syringe containing saline solution was administered simultaneously. The initial dose of continuous infusion was 1 mg/kg/hr, adjusting the dosage to achieve the desired sedation level. To induce sedation, an initial bolus of 0.50 mg/kg was administered in 5 mins. It was repeated in those cases in which it was considered clinically indicated. Midazolam (Dormicum®, 8-chloro-6- [2 flurophenyl]-1-methyl-4H imidazo [1,5-a] [1,4] benzodiazepine hydrochloride; Productos Roche SA, Madrid, Spain) as sole agent, was administered in an aqueous solution containing a concentration of 2 mg/mL. A placebo syringe containing a soya oil-based emulsion (Intralipid 10%®, Fides Laboratories, Barcelona, Spain) was administered

Table 1. Glasgow Coma Score modified by Cook and Palma (9)

Eyes Open	
Spontaneously	4
To speech	3
To pain	2
None	1
Response to Nursing Commands	
Obey commands	5
Purposeful movement	4
Nonpurposeful flexion	3
Nonpurposeful extension	2
None	1
Cough	
Spontaneous strong	4
Spontaneous weak	3
On suction only	2
None	1
Respiration	
Obey commands	5
Spontaneous intubated	4
SIMV/triggering	3
Respiration against ventilator	2
No respiratory efforts	1

SIMV, synchronized intermittent mandatory ventilation.

simultaneously. The initial infusion dose was 0.05 mg/kg/hr, adjusting the dosage to achieve the desired sedation level. To induce sedation, an initial bolus of 0.05 mg/kg was administered in 5 mins. It was repeated in those cases in which it was considered clinically indicated. Synergistic sedation consisted of propofol, at the initial infusion dose of 0.50 mg/kg/hr, combined with midazolam at the initial infusion dose of 0.03 mg/kg/hr, adjusting the dosage to achieve the desired sedation level. To induce sedation, an initial bolus of 0.20 mg/kg of propofol and 0.01 mg/kg of midazolam was administered in 5 mins. It was repeated in those cases in which it was considered clinically indicated. All patients received an analgesic morphine infusion (0.015 mg/kg/hr) and additional bolus doses (0.015 mg/kg) during potentially painful procedures.

The level of sedation was determined, on a continuous basis, by the nurse caring for the patient. The nursing staff adjusted the doses of all drugs during intravenous infusion by varying the doses by 20% increases or decreases to maintain the level of sedation within the range previously considered adequate.

Total dosages of propofol, midazolam and morphine, number of dosage modifications, cardiac frequency, systemic arterial pressures, central venous pressure, left atrial pressure, and sedation scores were assessed at 5-min intervals for the first 30 mins, then every 10 mins for the first hour, and finally every hour or more often if indicated. Hourly urine production was recorded. Transdermal continuous oxygen saturation was controlled by pulse oximetry as well as end-tidal CO_2 pressures. Blood gas analyses for arterial, venous, and central blood samples were performed every 8 hrs, or more frequently, if indicated. Other laboratory measurements were determined at admission and every 12 hrs, including hemoglobin, white blood cell count, platelets, blood glucose, urea nitrogen, creatinine, electrolytes, and triglycerides. Serum creatinine phosphokinase, lactate dehydrogenase, and aspartate aminotransferase concentrations were measured at admission and every 6 hrs thereafter. Any requirements for supplemental inotropes, vasopressors, vasodilators, and other drugs were also recorded.

Patients were mechanically ventilated with controlled mechanical ventilation at an initial respiratory rate of 10 breaths/min with a tidal volume of 12 mL/kg. According to the arterial blood gas measurements, tidal volume, respiratory rate, and F_{IO_2} were adjusted to maintain Pa_{O_2} of >70 torr (>10 kPa), and pH and P_{CO_2} values within normal range, without the addition of positive end-expiratory pressure.

Post sedation recuperation was determined every 5 mins, and included time from interruption of sedation up to response to simple orders, recuperation of effective spontaneous respiration and start of respirator disconnection, extubation, recuperation at a level of GCSC reactivity of >16 points (total recuperation), participation in physiotherapeutic program, drainage extraction, and sitting down. Mechanical ventilation was disconnected if the patient maintained a Pa_{O_2} of ≥70 torr (≥10 kPa), with an F_{IO_2} of ≤0.4, maintained current volumes of >4 mL/kg, showed respiratory frequency of 10 to 25 breaths/min, and did not present clinical signs of respiratory musculature fatigue or hemodynamic impairment. All patients who received a mixture of air enriched with oxygen through a T-tube were disconnected from the respirator.

Sample size was calculated according to the Altman nomogram (10), which is based on previous knowledge of clinically relevant differences observed in the hypothesis variables, significant level of 1%, and power of 90%. Assuming an exclusion rate of 15%, we planned a sample of 60 patients. Data were expressed as mean ± SD. Statistical analysis was performed by chi-square test or Fisher's exact test for nominal data. For other data, the unpaired Student's *t*-test was used to compare means between groups where the data could reasonably be assumed to be normally distributed; otherwise, the Mann-Whitney U test was used. Linear regression analysis was used to correlate sedation time and extubation time. A $p < .05$ was considered statistically significant.

RESULTS

Characteristics of Patients. Seventy-five patients were admitted to the study. Twenty-five patients received propofol as sole agent, 25 patients were sedated with midazolam as sole agent, and 25 patients received combined sedation with propofol and midazolam.

There were no statistically significant differences in age, gender, weight, % deviation of theoretical weight, ASA class, history of hypertension, prior myocardial infarction, previous bypass surgery, cardiopulmonary bypass time, and number of coronary artery bypass grafts (Table 2).

Analgesic and Sedative Requirements. Morphine maintenance doses and supplementary bolus were similar in all groups (Table 3).

Patients required sedation at 1.8 ± 1.2 hrs after admission to the ICU. No statistically significant differences were detected regarding duration of sedation for all groups. The mean induction and maintenance doses of propofol and midazolam as sole agents were 2.5 times higher than when both agents were used together. Patients sedated with a sole agent required 2.5 times higher supplementary boluses of propofol and four times more midazolam than did patients treated with the synergistic regimen. In addition, the total amount of sedative requirements was 3.5 times higher in patients treated with propofol and eight times higher in patients treated with midazolam than it was in those patients who received synergistic sedation (Table 3).

Quality of Sedation. During the first hour of sedation, 178 assessments of sedation were made in the propofol group, 184 in the midazolam group, and 172 in the synergistic group. There were 275, 283, and 252 assessments thereafter, in the propofol, midazolam, and synergistic group, respectively. All sedative regimens achieved similar efficacy in percentage of hours of adequate sedation (93% for propofol, 88% for midazolam, and 90% for synergistic group, $p = .10$). The percentage of sedation hours reached in each sedation level is shown in Figure 1.

Hemodynamic Effects. After induction of sedation, both the propofol and midazolam groups had significant decreases in systolic blood pressure, diastolic blood pressure, left atrial pressure, and heart rate (Table 4). Patients in the synergistic group had significant bradycardia throughout the study period without impairment in other hemodynamic parameters. In the propofol group, hemodynamic impairment was

Table 2. Demographic characteristics of the study population

	Propofol (n = 25)	Midazolam (n = 25)	Propofol-Midazolam (n = 25)	p Value
Age (yr)[a]	66.8 ± 6.8 (43–80)	67.2 ± 7.1 (42–81)	66.7 ± 7.3 (40–81)	.23
Gender (M/F)	17/8	16/9	19/6	.22
Weight (kg)[a]	66.4 ± 13.2 (48–103)	69.7 ± 11.6 (51–101)	65.2 ± 17.4 (45–99)	.19
% of deviation of theoretical weight[a]	11 ± 3	13 ± 2	10 ± 1	.14
ASA class (I/II)[a]	22/3	21/4	23/2	.31
History of hypertension (%)	23	20	25	.22
Prior MI (%)	20	16	24	.11
Second bypass surgery (%)	8	10	9	.10
Cardiopulmonary bypass time (min)[a]	106.3 ± 43.3 (43–180)	113.9 ± 51.2 (52–195)	110.5 ± 40.2 (50–200)	.34
Number of CABGs[a]	2.6 ± 1.3 (2–4)	2.3 ± 2.0 (2–4)	2.8 ± 1.5 (2–4)	.56

ASA, American Society of Anesthesiologists; MI, myocardial infarction; CABG, coronary artery bypass graft.

[a]Mean ± SD.

Values in parentheses indicate ranges.

recovered after the first 30 mins of sedation, with bradycardia also persisting at the end of the study. After 15 mins of sedation with midazolam, all hemodynamic values were similar to baseline values.

Only two patients in the midazolam group presented transitory arterial hypertension (mean arterial pressure [MAP] of >100 mm Hg) which was easily controlled with nitroprusside.

Cardiovascular depression, defined as a decrease in MAP of >20%, limited the dose of sedation in seven patients treated with propofol and in five patients sedated with midazolam. There was no need to interrupt sedation in any case. Eight of these patients improved hemodynamic stability with provision of fluids, achieving left atrial pressures of up to 18 mm Hg. In the other four patients (three in the propofol group and one in the midazolam group), it was also necessary to administrate inotropic drugs (dopamine in doses ranging between 5 and 12 μg/kg/min) to correct hemodynamic impairment. The total amount of fluids and doses of inotropic drugs did not differ in the two groups. No patient in the synergistic group required hemodynamic reanimation due to the impact of sedative drugs. Figure 2 shows the evolution of MAP throughout the study.

Other Adverse Effects. No allergic reactions or other adverse effects were detected in any of the patients studied.

Mortality. No patient died during the course of the study.

Laboratory Studies. Laboratory data reflect similar post cardiopulmonary bypasses and subsequent fluid shifts during postoperative care in all groups. Hematologic parameters did not differ significantly from those observed at admission in any of the groups. No significant thrombocytopenia was detected. No significant differences were found among the three groups in inorganic phosphorus, sodium, and triglycerides. An increase of creatinine phosphokinase was observed but did not differ among groups. Urea and creatinine concentrations did not show appraisable modifications compared with those at admission, nor did the rest of the biochemical parameters, including triglyceride concentrations.

Recovery From Sedation. Patients sedated with propofol or synergistic regimen awoke sooner and could be extubated 2.5 and two times more rapidly, respectively, than those patients sedated with midazolam.

Patients sedated with midazolam presented a delay of ≥3 hrs in achieving the capability to participate in the autonomous physiotherapeutic program. However, further steps in the rehabilitation program (drainage extraction, and sitting down) were reached in a similar way in all groups. For this reason, data concerning time up to ICU discharge showed no significant intergroup differences (41.2 ± 6.2 hrs for propofol, 42.6 ± 8.9 hrs for midazolam, and 42.2 ± 6.7 hrs for synergistic sedation; $p > .05$) (Table 5).

The time elapsed up to extubation correlated statistically with treatment time in patients in the propofol group ($r^2 = .86$; $p < .01$). In the synergistic group, there was also a statistically significant correlation between these parameters (Fig. 3). Nevertheless, in the midazolam subgroup there was no relationship between sedation time and time to extubation ($r^2 = .16$; $p < .05$).

Cost of Sedation. Synergistic sedation allowed pharmaceutical cost savings of 28% with respect to midazolam and 68% with respect to propofol (Table 6).

DISCUSSION

The present study is, to our knowledge, the first comparison of propofol and midazolam carried out according to the double-blind method. However, the application of this methodology, in the study conditions, obliged us to resolve two previous problems. The first practical problem was the easy visual identification of the sedative drugs, due to the very clear differences between propofol, whose excipient is a lipidic solution, and midazolam, which is diluted in saline solution. This motivated the use of a methodologic technique called double dummy (simultaneous injection of two syringes with propofol and midazolam in the synergistic group, midazolam and lipidic emulsion as placebo in the midazolam group, and propofol and saline solution as placebo in the propofol group). A secondary ethical problem was to determine whether lipidic emulsion could be considered a placebo. Our Ethics and

Table 3. Comparison of time of sedation and doses of sedatives (mean ± SD)

	Propofol (n = 25)	Midazolam (n = 25)	Propofol-Midazolam (n = 25)	*p* Value
Time of sedation (hr)	14.4 ± 1.5	14.1 ± 1.1	14.7 ± 1.9	.29
Mean maintenance dose of morphine (mg/hr)	1.0 ± 0.70	1.4 ± 0.8	1.1 ± 0.8[a]	.42
Number of supplementary bolus doses of morphine	1.2 ± 0.5	1.8 ± 0.3	1.4 ± 0.2	.38
Mean induction dose of sedative agents (mg/kg)	0.55 ± 0.05	0.05 ± 0.01	0.22 ± 0.03[a] 0.02 ± 0.00[b]	.001[c] .001[c]
Mean maintenance dose of sedative agents (mg/kg/hr)	1.20 ± 0.03	0.08 ± 0.01	0.50 ± 0.09[a] 0.03 ± 0.01[b]	.001[c] .001[c]
Number of supplementary bolus doses of sedatives	1.3 ± 0.5	2.2 ± 0.9	0.5 ± 0.0	.03[c]
Total amount of sedative agents (mg)	1197.4 ± 27.2	88.6 ± 9.7	321.6 ± 27.5[a] 10.4 ± 9.7[b]	.001[c] .001[c]

[a]In reference to propofol; [b]in reference to midazolam; [c]comparing the third column with the others.

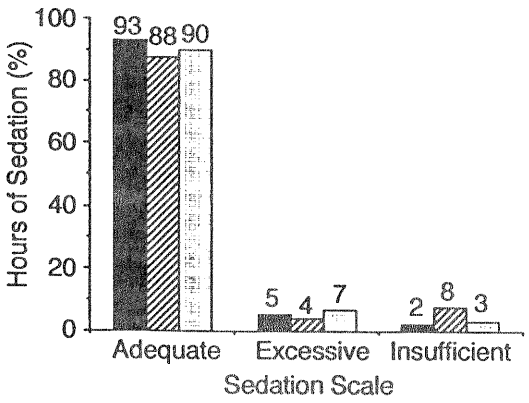


Figure 1. Quality of sedation according to sedation scale (see Materials and Methods) with propofol (*solid bar*), midazolam (*hatched bar*), and propofol-midazolam (*gray, dotted bar*). No statistically significant differences among groups were observed.

Research Committee evaluated and approved both proposed solutions at the same time as the remainder of the methodologic guidelines.

The main finding of this study is that, all sedatives being equally effective, synergistic sedation was associated with a shorter weaning period than midazolam and lower hemodynamic impact and drug requirement than the other regimens, resulting in a safer and more favorable economic profile. Therefore, the four points of our initial hypothesis can be considered confirmed according to the following points.

In reference to the first point of the hypothesis, to analyze the efficacy of sedative, it was necessary that we comply with the design conditions. These conditions included avoiding that morphine coadministration be a

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counfounding variable, establish a rational dosage of the new synergistic treatment, and use a validated method to assess level and quality of sedation.

Morphine maintenance and bolus doses were similar in the three groups. Patients received a fixed scheme adjusted to the weight of this agent because they could not answer any questions about their level of pain. This absence of intergroup differences in analgesic treatment, and the accurate standarization and stratification of groups, avoided that this cotreatment would be a confounding variable.

Our goal was to attain a deep level of sedation (without patient response to commands), thus explaining the differences in morphine requirements, with other studies. Higgins et al. (5) observed that, in patients responsive to commands, 53% of those sedated with midazolam requested morphine, while a significantly lower number of patients sedated with propofol (33%) required it.

Regarding sedative requirements, the deep sedation of our patients also explains their higher requirements for propofol and midazolam in single administration than those communicated by other authors (5) whose patients were less deeply sedated.

Available data concerning induction and maintenance doses for synergistic sedation are difficult to compare

Table 4. Hemodynamic variables at baseline and after the induction of sedation (mean ± SD)

Hemodynamic Variable	Baseline	10 Mins	30 Mins	Mean[a]
SBP (mm Hg)				
Propofol	114 ± 20	98 ± 19[b]	99 ± 18[b]	111 ± 33
Midazolam	112 ± 18	100 ± 14[b]	105 ± 16	110 ± 29
Propofol-Midazolam	113 ± 19	108 ± 15	112 ± 18	111 ± 25
DBP (mm Hg)				
Propofol	75 ± 16	62 ± 11[b]	64 ± 13[b]	72 ± 23
Midazolam	73 ± 15	63 ± 10[b]	71 ± 14	73 ± 14
Propofol-Midazolam	74 ± 17	72 ± 14	75 ± 19	72 ± 19
LAP (mm Hg)				
Propofol	11 ± 7	6 ± 5[b]	7 ± 6[b]	12 ± 6
Midazolam	11 ± 6	7 ± 6[b]	12 ± 6	11 ± 7
Propofol-Midazolam	11 ± 7	10 ± 7	11 ± 5	12 ± 5
Heart Rate (beats/min)				
Propofol	110 ± 22	86 ± 26[b]	87 ± 29[b]	93 ± 35[b]
Midazolam	106 ± 19	86 ± 29[b]	104 ± 27	112 ± 32
Propofol-Midazolam	114 ± 19	82 ± 21[b]	92 ± 23[b]	95 ± 23

SBP, systolic blood pressure; DBP, diastolic blood pressure; LAP, left atrial pressure.
[a]Mean values of all subsequent determinations until the end of the study; [b]$p < .05$ with respect to baseline values.

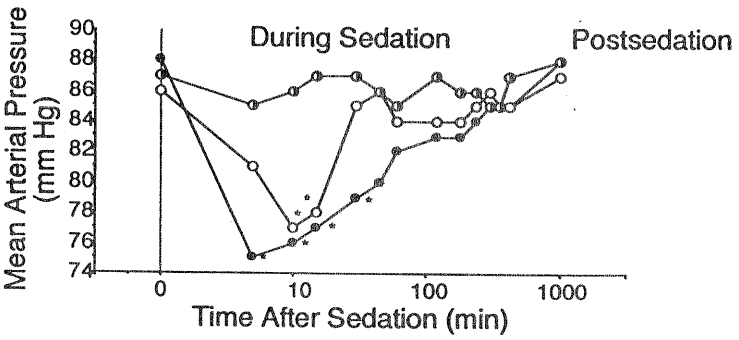


Figure 2. Mean arterial pressure vs. time expressed as log 10 scale to compress data without loss of detail in early measurements. Data points correspond to start of sedation, 5 10, 15, 20, and 30 mins, and 1, 2, 4, 6, 8, 10, 12, and 14 hrs of sedation. *Solid circles*, propofol; *open circles*, midazolam; *half solid, half open circles*, propofol-midazolam. *Statistically significant ($p < .05$).

because they come from anesthetic studies, which analyze the administration of bolus injection in noncritically ill patients. Short and Chui (11) and McClune et al. (8) have found that, when midazolam and propofol were administered simultaneously for hypnosis (clinical end point: loss of response to verbal command) during the induction of anesthesia, the mean effective dose (ED50) for the combination was up to 50% less (range 25% to 44% for midazolam, and 44% to 50% for propofol) than that expected from ED50 values of the individual agents. Facing the lack of valid references in medical literature, we established the ratio of propofol and midazolam doses in the synergistic regimen according to data from our previous studies, suggesting that to achieve equipotent maintenance doses of midazolam about 13 times more propofol than midazolam is needed (12). In the present study, we observed a reduction of >68% in both mean maintenance doses when they were administered together. Also, we observed a similar reduction in total amount and in the mean number of supplementary boluses required by synergistic sedation, reflecting a more stable sedation and confirming the synergism between the two agents during continuous sedation of ICU patients (13). However, the mechanism of this synergism has not been determined. Clinical results refute a pharmacokinetic cause for the synergism because the alteration in free plasma concentration of either of these drugs when they are administered together has not been demonstrated (11). In the absence of definitive studies, the most accepted cause is a pharmacodynamic interaction at a gamma-aminobutyric acid α-receptor in the brain.

In the assessment of quality of sedation, we employed the GCSC as the sedative scale because it showed better objectivity, reproducibility, and interobserver agreement than did the Ramsay scale in a previous study done by our group (13). Although the Ramsay scale is the most widely employed sedative scale, it is based on a clinical end point that can imply subjectivity (14). On the other hand, the GCSC uses a reactivity-conscience scale adapted to ventilated patients, which achieves better validity for ICU patients (15).

All sedative regimens achieved similar efficacy in percentage of hours of adequate sedation (93% for propofol, 88% for midazolam, and 90% for synergistic groups, respectively). These results concur with those of previous studies by our group (11), but they are better than those observed by other authors who used Ramsay scale, such as Aitkenhead et al. (16) (84% for propofol and 72% for midazolam) or Higgins et al. (5) in which nurses were able to maintain patients at level 3 of the Ramsay scale only 60% of the time. These differences can be attributed to the use of different scales and different goals of sedation.

Regarding the second point of the hypothesis, our results confirm previous findings concerning hemodynamic effects of both propofol and midazolam administered as sole agents. Although baseline hemodynamic values were comparable, after induction of sedation both the propofol and midazolam groups had significant decreases in systolic blood pressure, diastolic blood pressure, left atrial pressure, and heart rate. In the propofol group, these depressive effects recovered after the first 30 mins of sedation but significant bradycardia persisted. In the midazolam group, recuperation occurred after 15 mins of sedation, including bradycardia. These findings concur with those of other authors (17–19). Published data concerning the hemodynamic effects of propofol, such

Table 5. Comparison of extubation and total recovery time (mean ± SD)

	Propofol (n = 25)	Midazolam (n = 25)	Propofol-Midazolam (n = 25)	*p* Value[a]
Time to extubation (hr)	0.9 ± 0.3	2.3 ± 0.8	1.2 ± 0.6	.01
Total recovery time (hr)	1.3 ± 0.5	3.8 ± 1.8	1.6 ± 0.8	.01
Capacity for autonomous physiotherapeutic program (hr)	2.8 ± 2.5	6.3 ± 4.3	3.3 ± 1.9	.01
Drainage extraction (hr)	35.3 ± 4.2	38.2 ± 6.2	36.7 ± 3.9	.06
Able to sit down (hr)	38.3 ± 5.3	40.2 ± 7.0	38.8 ± 6.1	.09

[a]Reflects differences between the second column and the other two columns.

Table 6. Comparison of pharmaceutical cost of sedatives (mean ± SD)

	Propofol (n = 25)	Midazolam (n = 25)	Propofol-Midazolam (n = 25)	*p* Value
Cost of sedation (pesetas)	102.2 ± 0.1	59.2 ± 11.8	62.2 ± 6.5	.03[a]
Cost of maintenance and supplementary doses (pesetas)	3249.4 ± 75.9	1447.0 ± 153.1	1014.6 ± 235.4	.02[b]
Total cost of sedatives (pesetas)	3351.6 ± 76.0	1506.2 ± 164.9	1076.8 ± 241.9	.001[b]

[a]In reference to propofol; [b]comparing the third column with the others.
$1 = 135 pesetas, at time of study.

as the study by Claeys et al. (17) in ten ASA I patients scheduled for total hip replacement, showed that after infusion of propofol, systemic arterial pressure decreased by 30% in systolic arterial pressure, and by 25% in diastolic arterial pressure. These changes were accompanied by a decrease of 31% in systemic vascular resistances without changes in cardiac index and adequate relation between left ventricular systolic work and pulmonary artery occlusion pressure. Other authors, such as Higgins et al. (5) who studied populations similar to ours, also observed a transient 20 mm Hg decrease in MAP after bolus administration, motivating a reduction in bolus doses (initial bolus of 0.5 to 0.25 mg/kg). Available data concerning hemodynamic effects of midazolam reported that, although midazolam has minimal hemodynamic effects in healthy subjects, significant decreases in blood pressure have occurred in hypovolemic and elderly patients (18). These results agree with those communicated by Snellen et al. (19) in 40 patients after bypass coronary intervention, who observed a transient 19% mean decrease in MAP at 10 mins after starting midazolam. In addition, conventional sedation had a low incidence of severe arterial hypotension requiring treatment (in seven patients treated with propofol and five patients treated with midazolam). This impairment was easily corrected with inotropics and/or plasmatic volume expansion. Since neither synergistic induction nor synergistic maintenance regimes caused arterial hypotension, and no patient required hemodynamic reanimation, its use in hemodynamically unstable patients can provide a clinical advantage with respect to conventional sedation.

These findings focused on the optimal duration of sedative bolus injection to prevent arterial hypotension. Stokes and Hutton (20) observed that

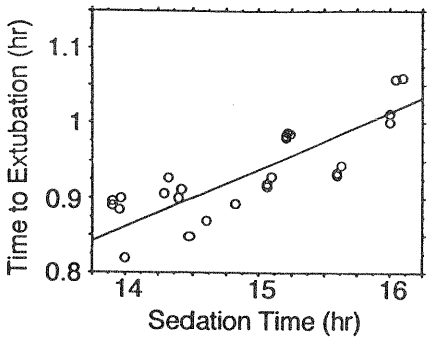


Figure 3. Correlation between sedation time and interval up to extubation in patients sedated with propofol and midazolam administered together. $r^2 = .78$; $p < .01$.

the dose of propofol required to induce anesthesia decreased when slower rates were used, and slow infusion rates caused less depression of blood pressure than did rapid infusion. Our previous study (13) confirmed this finding and showed that the minimum time of bolus injection which does not induce hemodynamic changes in stable patients is 5 mins.

Our results confirm the decrease in heart rate produced by propofol and synergistic sedation. Since there are clinical data suggesting a relationship between persistent tachycardia and postoperative coronary ischemia, the bradycardia observed in both the propofol and the synergistic groups can also be considered a clinical advantage.

Previous studies (7, 21) have shown that postoperative hypertension occurs in 30% to 50% of patients after coronary surgery. In our study, only two patients in the midazolam group presented postoperative hypertension. Previous investigations have postulated that this effect can be due to activation of a pressor reflex from the heart and great vessels and that it can be avoided with the block of stellate ganglion (21). These differences could be due to a different surgical technique and a different definition of arterial hypertension. However, these findings require further specific study.

This study confirms that the three sedative regimes can be considered safe with respect to induction of adverse effects, with the exception of cardiovascular depression.

The third point of the hypothesis was that synergistic sedation provides a fast recovery time similar to propofol and faster than midazolam. Our results showed that mean recovery time

until extubation in the propofol and synergistic sedation groups was two times lower than that observed in patients treated with midazolam. Fast recovery after discontinuation of propofol is considered a clinical advantage over midazolam by several authors (16, 22). Contrarily, in the study by Higgins et al. (5), there are no differences between the two drugs with respect to time to extubation. However, as the authors (5) recognize, this fact can be due to the residual effect of higher doses of opioids administered during operative anesthesia. In our study, we waited for the patients to reach GCSC 12 points before starting sedation. This fact acted as a washout period eliminating the possible intergroup differences from the residual effects of hypnotics and opioids received intraoperatively.

With respect to the effect of sedatives on weaning, the correlation between time of sedation and time required until extubation observed in propofol and synergistic sedation administration was highly significant. In the midazolam group, time to extubation could not be predicted. The inferior recovery variability after propofol use is considered to be an additional clinical advantage, which is also present in synergistic sedation.

Although patients in the propofol and synergistic groups showed faster recovery that improved rehabilitation treatment, evidence of better results was only observed in the first 12 hrs. The following steps in the rehabilitation program were reached in a similar way in all groups, reflecting the disappearance of residual effects of sedatives after 12 hrs of discontinuing sedation and motivating no differences in length of ICU stay.

The fourth point of the hypothesis referred to the cost of sedative treatment. The results of the current study indicate that synergistic sedation produced a savings of >400 pesetas (at time of study, $1 = 135 pesetas) (28%) with respect to midazolam, and a savings of >2200 pesetas (68%) with respect to propofol. These savings in pharmaceutical costs are due to the use of smaller doses. However, a specific pharmaco-economic analysis was not possible because we did not record other important variables, such as the cost of post sedation care.

In summary, we believe that in the conditions of this study, the new synergistic treatment with propofol and midazolam administered together, is an effective and safe alternative for sedation with some advantages over the conventional regimen of propofol or midazolam administered as sole agents, such as absence of hemodynamic impairment, a >68% reduction in maintenance dose, and less pharmaceutical cost.

It would be advisable to carry out other large, double-blind, multicenter studies, which could validate our results and evaluate the efficacy and safety of this new treatment in medium- and long-term sedation of critically ill patients with different clinical conditions.

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