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A. A. Weinbroum
P. Halpern
V. Rudick
P. Sorkine
M. Freedman
E. Geller[1]

Midazolam versus propofol for long-term sedation in the ICU: a randomized prospective comparison

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A. A. Weinbroum · V. Rudick · P. Sorkine · M. Freedman · E. Geller
Departments of Anesthesiology and Critical Care Medicine, Tel-Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel-Aviv University, Israel

P. Halpern (✉)
Department of Emergency Medicine, Tel-Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel-Aviv University, 6 Weizman Street, Tel-Aviv 64239, Israel,
FAX: + 972 (3) 697 4670

[1] *Present address:*
Surgical Intensive Care Unit, Palo Alto Veterans Administration Medical Center and Stanford University School of Medicine, Palo Alto, CA, USA

Abstract *Objective:* To compare the efficacy, safety, and cost of midazolam and propofol in prolonged sedation of critically ill patients.
Design: Randomized, prospective study.
Setting: General intensive care unit (ICU) in a 1100-bed teaching hospital.
Patients: 67 critically ill, mechanically ventilated patients.
Interventions: Patients were invasively monitored and mechanically ventilated. A loading dose [midazolam 0.11 ± 0.02 (SEM) mg · kg^{-1}, propofol 1.3 ± 0.2 mg · kg^{-1}] was administered, followed by continuous infusion, titrated to achieve a predetermined sedation score. Sedation was continued as long as clinically indicated.
Measurements and results: Mean duration of sedation was 141 and 99 h (NS) for midazolam and propofol, respectively, at mean hourly doses of 0.070 ± 0.003 mg · kg^{-1} midazolam and 1.80 ± 0.08 mg · kg^{-1} propofol. Overall, 68 % of propofol patients versus 31 % of midazolam ($p < 0.001$) patients had a > 20 % decrease in systolic blood pressure after the loading dose, and 26 versus 45 % ($p < 0.01$) showed a 25 % decrease in spontaneous minute volume. Propofol required more daily dose adjustments (2.1 ± 0.1 vs 1.4 ± 0.1, $p < 0.001$). Nurse-rated quality of sedation with midazolam was higher (8.2 ± 0.1 vs 7.3 ± 0.1 on a 10-cm visual analog scale, $p < 0.001$). Resumption of spontaneous respiration was equally rapid. Recovery was faster after propofol ($p < 0.02$), albeit with a higher degree of agitation. Amnesia was evident in all midazolam patients but in only a third of propofol patients. The cost of propofol was 4–5 times higher.
Conclusions: Both drugs afforded reliable, safe, and controllable long-term sedation in ICU patients and rapid weaning from mechanical ventilation. Midazolam depressed respiration, allowed better maintenance of sedation, and yielded complete amnesia at a lower cost, while propofol caused more cardiovascular depression during induction.

Key words Midazolam · Propofol · ICU · Prolonged sedation

Introduction

Critically ill, ventilated patients usually require sedation. Sedation improves tolerance of the endotracheal tube and of invasive procedures, facilitates mechanical ventilation, blunts excessive hemodynamic and metabolic responses, and allays anxiety [1–4]. Midazolam has been successfully used for prolonged sedation [5, 6], due to its relatively short elimination half-life, lack of accumulation of active metabolites [7], and induction of amnesia [5]. Propofol is a rapidly acting general anesthetic agent [8]; recovery is fast as well.

Data regarding the efficacy, safety, tolerability, and detailed cardiorespiratory effects of propofol as a continuous long-term (> 24 h) sedative agent, and its cost in the intensive care unit (ICU) are becoming more available. The majority of the earlier clinical trials compared propofol to midazolam, administered either continuously or by intermittent boluses, mostly in postcardiac surgery patients and for a period of ≤ 24 h [9–12]. Most authors concluded that propofol was superior to midazolam in sedating ICU patients. The present study compared the relative safety, efficacy, and cost-effectiveness of midazolam and propofol for prolonged (> 24 h) sedation of critically ill patients admitted to a general ICU.

Patients and methods

This investigation was approved by the Institutional Human Studies Review Committee, and informed written consent was obtained from the patients or next of kin. Sixty-seven consecutive, critically ill patients requiring mechanical ventilation were enrolled within 1 h of arrival in the ICU. The Acute Physiology and Chronic Health Evaluation II scoring system was employed in assessing the severity of the patients' conditions.

Patients were assigned to receive midazolam or propofol according to a computer-generated randomization schedule. A loading dose of the selected drug was first administered by slow (2–5 min) manual injection via a central venous catheter. The dose was titrated to achieve a level of sedation of 2–3 on a five-point sedation scale: 1 = awake; 2 = drowsy, responds to verbal stimulation; 3 = asleep but awakens to mild tactile stimulation; 4 = asleep, responds to painful stimulation only; 5 = deeply asleep, does not respond to painful stimulation (modified from [13]). Patients were also evaluated at each sedation level as to whether they were agitated (–) or calm (+). Midazolam was given in a concentration of 30 mg · 100 ml^{-1} saline, and propofol (Diprivan, ICI Pharmaceuticals, Macclesfield, UK) was given undiluted in the original 1% concentration. Immediately after the desired level of sedation was achieved, a continuous infusion of the assigned drug was started using a constant-rate peristaltic infusion pump. Prior to induction and 5, 10, 15, 30, 45, and 60 min following induction, the degree of sedation and the presence or absence of agitation, as well as the other tested parameters were recorded. The initial hourly maintenance dose was equal to the induction dose; the subsequent rate of infusion was titrated to maintain the desired 2–3 sedation level and calmness, as assessed hourly by the attending nurse. The infusion rate could be readjusted by ± 50% of the existing dose rate in order to maintain the pre-established degree of sedation or to allay agitation. Physical restraints were used if the patient had a sedation score greater than 4 but was still agitated. This was a very rare combination. The sedation protocol is the standard clinical sedation protocol in use in our unit, in which, prior to the present study, midazolam was normally given.

At the end of each shift, the nurse attending the patient recorded an efficacy assessment of the overall quality of sedation on a linear visual analog scale from 1 (totally unsatisfactory) to 10 (optimal) based on the patient's response to endotracheal tube suctioning, dressing changes, and repositioning, as well as reaction to the ICU environment. Morphine sulfate was administered intravenously in 2-mg increments for pain control. Bronchodilators (intravenous aminophylline and nebulized salbutamol) or vasoactive drugs were also prescribed by the attending physician when indicated.

Infusion of the sedative drug was discontinued when patients were judged to be ready for extubation. Assessment was continued for 3 h thereafter.

After initiation of sedation, patients were ventilated in the synchronous intermittent mandatory ventilation (SIMV) mode with 5 cm H_2O positive end-expiratory pressure and 7 cm H_2O pressure support, using a Puritan-Bennett 7200 (Puritan Bennett UK, Hounslow, Middlesex) or an Engstrom Erica (Engstrom Medical, Bromma, Sweden) ventilator. Normocapnia was maintained and the partial pressure of oxygen in arterial blood (PaO_2) was kept between 70 and 100 mmHg. All patients had indwelling arterial, central venous (CVP) and urinary catheters. Arterial pressure, oxygen saturation, heart rate (HR), CVP, and expired CO_2 were continuously measured (Mennen Medical XL Series, Rehovot, Israel). Respiratory rate (RR), tidal and minute volumes, and core temperature, urinary output, and fluid balance were recorded hourly.

During the first day of maintenance infusion, the patients were shown simple pen drawings. One hour later they were asked to identify them. Three hours after extubation, patients were again asked to identify these items and to describe any events they recalled during the period of sedation.

In patients considered fit for weaning from mechanical ventilation, the SIMV rate was gradually decreased to zero [i.e., to continuous positive airway pressure (CPAP)] while patients were still sedated. The rate of decrease of SIMV was determined by the physician directly in charge of the patient, regardless of the sedative drug used.

All data are expressed as mean ± SEM with 95% confidence intervals (CI). Statistical analysis was performed using the chi-square test for nonparametric data, and repeated analysis of variance (RANOVA) for parametric variables. A p value of less than 0.05 was considered significant.

Results

Table 1 gives details of the patients' characteristics and admission diagnosis. At no time was there a need to discontinue either drug because of side effects, and none of the enrolled patients died during the study period. Table 2 summarizes the various parameters used to assess the quality of sedation. All patients achieved the desired degree of sedation within 5 min of receiving the loading dose of the assigned drug. During maintenance infusion, patients in both groups were sedated to the same degree. The average number of hours per day when patients exceeded the desired sedation score range was also similar. Propofol patients were more agitated during maintenance, although sedation was rated as being adequate. The infusion readjustment rate was lower for midazolam, and nurses' ratings were significantly higher for midazolam (Table 2). There was no evidence of tachyphylaxis during the maintenance period.

Recovery from sedation was significantly faster after propofol, starting 30 min after it was discontinued, with patients fully awake within 1.8 ± 0.4 (1.02–2.58 CI) h, compared to 2.8 ± 0.4 (2.02–3.58) h for midazolam ($p < 0.02$). However, more propofol patients than midazolam patients were agitated between 30 and 60 min

Table 1 Patients' general data. Data are means ± SEM (95 % confidence intervals) (*APACHE* Acute Physiology and Chronic Health Evaluation)

[a] Main admission diagnosis. The groups were matched so that there was no statistical significance (p = NS)

Variable	Midazolam	Propofol
No.	36	31
Age (years)	51 ± 6 (39–63)	56 ± 3 (50–62)
Weight (kg)	70 ± 2 (66–74)	71 ± 2 (67–75)
Sex (M/F)	12/24	10/21
APACHE II (on admission)	17 ± 1 (15–19)	18 ± 2 (14–22)
Respiratory failure/multiple trauma/ post major surgery[a] *(n)*	2/9/25	2/9/20
Duration of sedation (h)	141 ± 27 (88–194)	99 ± 15 (70–128)
Duration of stay in ICU (days)	31 ± 7 (17–45)	21 ± 4 (13–29)

Table 2 Sedation data during maintenance infusion. Data are means ± SEM (95 % confidence intervals)

[a] $p < 0.05$ versus preinduction values
[b] $p < 0.01$ between the groups
[c] $p < 0.001$ between the groups

Parameter	Midazolam	Propofol
Sedation score before induction	1.4 ± 0.1 (1.2–1.6)	1.3 ± 0.1 (1.2–2.48)
Loading dose (mg · kg^{-1})	0.11 ± 0.02	1.3 ± 0.2
Hourly maintenance infusion rate (mg · kg^{-1})	0.07 ± 0.003	1.8 ± 0.08
Mean maintenance sedation score	2.2 ± 0.1[a] (2.0–2.4)	2.3 ± 0.1[a] (2.1–2.5)
Agitation (hours · day^{-1})	1.7 ± 0.2 (1.31–2.09)	2.6 ± 0.3[b] (2.01–3.19)
Infusion rate readjustments · day^{-1}	1.4 ± 0.1 (1.2–1.6)	2.1 ± 0.1[c] (1.9–2.3)
Nurses' 8-hourly rating	8.2 ± 0.1 (8.0–8.4)	7.3 ± 0.1[c] (7.1–7.5)

Table 3 Additional (nonsedative) drug administration

Drug	Midazolam[a,b]	Propofol[a,b]
Morphine (mg · day^{-1})	8 ± 1 (6.04–9.96) (*n* = 30)	11 ± 3 (5.12–16.88) (*n* = 22)
Bronchodilators (% of time)	21 (*n* = 15)	19 (*n* = 7)
Regular insulin infusion (% of time)	15 (*n* = 14)	19 (*n* = 9)

[a] Drug data are menas ± SEM (95 % confidence intervals). There was no statistical significance between the groups (p = NS)
[b] n = number of patients

after sedation was discontinued, (27 and 18 %, respectively, at 45 min, $p < 0.05$, and 35 and 10 %, respectively, at 60 min, $p < 0.02$). A few propofol patients required moderate physical restraints for ~ 2 h.

Both midazolam and propofol patients required similar mean daily dosages of morphine for pain control (Table 3). The average duration of vasoactive support and the number of patients requiring intravenous aminophylline and nebulized salbutamol for the treatment of bronchospasm were similar (Table 3).

Hemodynamic and respiratory variables were similar between the groups before the initiation of sedation (Figs. 1, 2). Five minutes after the beginning of induction, propofol caused a greater fall in mean blood pressure (MBP) (Fig. 1). Blood pressure in the propofol group did not return to preinduction values until > 60 min after induction. Eleven midazolam patients (31 %) and 21 propofol patients (68 %) showed a drop greater than 20 % in systolic blood pressure (SBP) ($p < 0.05$ within the group, $p < 0.001$ between the groups). Thirteen (42 %) propofol patients versus 1 (3 %) midazolam patient ($p < 0.01$) and 6 (19 %) propofol versus none of the midazolam group ($p < 0.0001$) showed a drop in SBP to ≤ 90 mmHg at 5 and 15 min postinduction, respectively, while in 12 (39 %) propofol patients and 1 (3 %) midazolam patient ($p < 0.02$) diastolic blood pressure dropped below 50 mmHg within the 1st h after induction. Twenty-one (68 %) propofol patients versus 5 (14 %) midazolam patients ($p < 0.001$) required volume loading of more than 350 ml to prevent a decline in SBP to below 80 mmHg. HR and CVP did not change significantly in either group following drug induction.

MBP, HR, and CVP were similar in the two groups during maintenance infusion. Complete blood counts, serum electrolyte concentrations, liver and renal function tests, and coagulation profiles were similar in the two groups, as was mean total fluid balance. Six patients in each group required veno–venous hemofiltration for 1.5–2.5 days.

Following the induction of sedation, propofol caused a fall in RR (Fig. 2, bottom panel). There was a linear correlation between RR and spontaneous minute ventilation in the propofol group ($r^2 = 0.99, p = 0.0001$). Midazolam induced a decrease in both RR and minute ven-

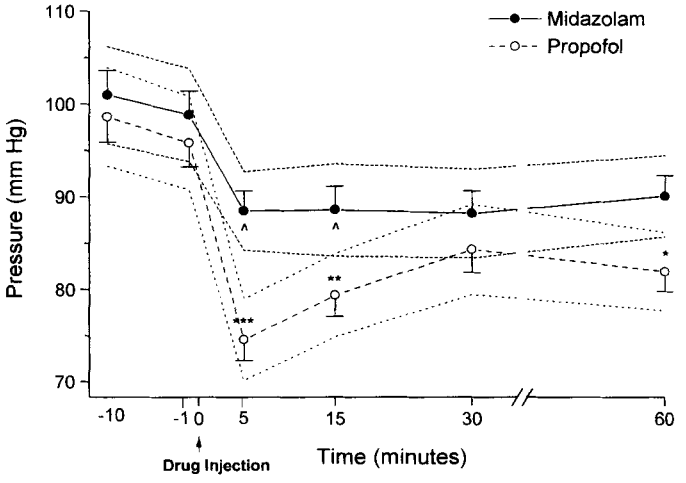

Fig. 1 Changes in mean arterial blood pressure following induction of sedation. Data are expressed as means ± SEM with 95 % confidence intervals. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus pre drug injection values; ∧ $p < 0.05$ between the groups

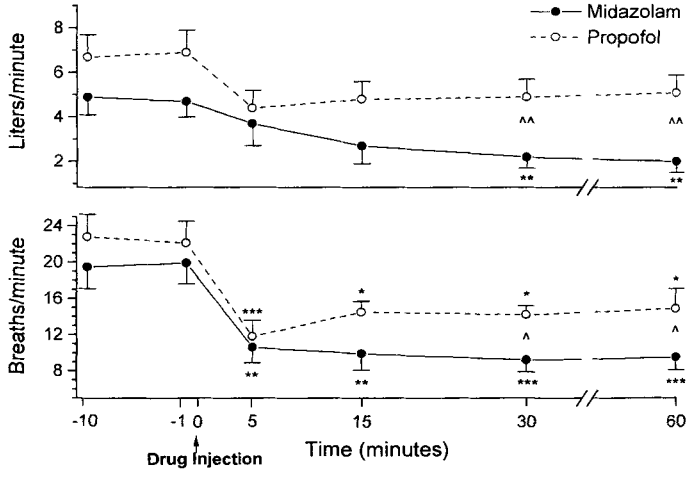

Fig. 2 Changes in respiratory rate *lower panel* and spontaneous minute ventilation *upper planel* following induction of sedation. Data are expressed as means ± SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus pre drug injection; ∧ $p < 0.05$, ∧∧ $p < 0.01$ between the groups. The 95 % confidence intervals were omitted in order to present data more clearly

tilation (Fig. 2). However, while propofol showed a slow but gradual return to preinduction values, starting at the 15-min time point, this did not happen in the midazolam patients for > 60 min after induction. PaO_2, SpO_2, expired CO_2, and blood bicarbonate levels did not change significantly in the two groups and remained similar in both during the entire study period, as did the SIMV rate.

While still on drug infusion, 20 midazolam and 19 propofol patients (NS) were successfully weaned off SIMV to CPAP on the first attempt, within 3.2 ± 1.0 (1.24–5.16) and 2.0 ± 1.7 (– 1.33 to 5.33) h respectively (NS). No significant changes in hemodynamic, metabolic, or respiratory variables were noted during the 3 h following discontinuation of either drug and there was no case of resedation among these patients. There was no correlation between weaning times and total infused drug doses.

Drug cost per patients was U.S. $ 164 ± 37 (91–240) in the midazolam group and U.S. $ 662 ± 150 (368–956) ($p < 0.001$) in the propofol group, while hourly drug costs were U.S. $ 1.19 ± 0.2 (0.8–1.58) and U.S. $ 6.24 ± 0.9 (4.48–8.0) respectively ($p < 0.001$).

Among the 18 midazolam patients tested for amnesia, none was able to recall the drawings shown to them while under the effect of the drug nor could they recall any event occurring during the study period. In contrast, 12 of 17 ($p < 0.001$) propofol patients recalled the drawings and could remember sporadic events from the study period.

Discussion

Desirable properties of sedative drugs for ICU sedation include rapid onset and short duration of action, rapid metabolism and elimination, absence of cardiorespiratory effects, being minimally affected by hepatic or renal dysfunction, and low cost. The need for continuous sedation in the ICU as well as the ideal level of such sedation remain controversial [14, 15]. It is, however, generally accepted that most mechanically ventilated patients require some sedation [16]. Drugs employed for this purpose include opiates, benzodiazepines, general anesthetics, and neuroleptics [14, 16].

Midazolam is commonly used for ICU sedation because it is anxiolytic, hypnotic, anticonvulsant, and a muscle relaxant. Propofol has been studied for sedation in the ICU, but few studies have documented its use for long periods and none have documented its effects after the sedation period. Our findings address these issues and partly differ from previous data [9, 12, 17, 18] wherein propofol was considered superior to midazolam, as judged by the duration of time sedation was maintained at the desired level. This conclusion is, however, open to question: in Ronan et al.'s study [12] there were significant differences in the level of sedation between the groups, and undisclosed doses of both drugs were administered as boluses before suctioning or application of dressings to patients. The present study demonstrated that both drugs were equally satisfactory for maintaining patients at a predetermined level of sedation. There were, however, differences in the degree of agitation, ease of establishing a stable sedation level, and amnesia between the two drugs which became evident. We feel that it was useful to add the observation

on the presence of agitation during sedation and the nurses' 8-hourly assessment, and that these supply additional dimensions to the quality of sedation. Admittedly, since the study was not blinded, a theoretical bias by the nurses may have been present. However, since there were more than two dozen nurses who could be randomly involved in the care of each patient during the stay in the ICU, the likelihood of bias is extremely remote. The sedation scale we used was a modification of the one first used to describe patients with barbiturate overdose, and we have employed it successfully since 1988 in over 200 sedated and oversedated patients [5, 19].

Other authors have used additional analgesics and employed various dosing methods [20–22] when comparing propofol with other sedatives in the ICU. This also makes comparisons between the drugs more difficult. Harper et al. [21], for example, studied propofol plus fentanyl in the ICU for up to 260 h of sedation in 44 patients. They noted rapid awakening (18 min), within a time frame much shorter than for data reported elsewhere [23], a difference not explained by the authors. We used no alternative drugs in the patients we studied, even when patients became agitated. Only morphine was used for analgesia, and bronchodilators and vasoactive drugs were prescribed by the attending physician. All these extra medications were matched in the two groups and therefore would not account for the time to awakening.

Induction of sedation with propofol was accompanied by rather marked and prolonged hypotension. Although previously documented, the present study further details the drugs' effects in both groups, mainly propofol. Monk et al. [24] found a significant decrease in blood pressure, cardiac output, and systemic vascular resistance following propofol administration. Brussel et al. showed that propofol had a negative inotropic effect, as evidenced by a 20 % decrease in blood pressure, a 17 % decrease in cardiac output, and a 16 % decrease in the peak rate of left ventricular developed force [22]. Newman et al. [25] also noted a significant cardiodepressant effect of propofol in critically ill patients. Decreased mean and diastolic blood pressures were also noted after initial loading of propofol in the study by Roekaerts et al. [10]. Moreover, a 20 % decrease in arterial pressure occurred when propofol was administered at a lower dose than that used in the present study [12]. Hemodynamic and respiratory effects of propofol in association with hypovolemia were found in dogs as well [26]. Other investigators, however, have reported no difference in hemodynamic and respiratory variables [17]. Since fluid and vasoactive requirements, as well as CVP, MBP, and HR were similar prior to induction of sedation, the hypotensive effect of propofol in the present study cannot be attributed to hypovolemia alone. This is of potential clinical importance and is in contrast to previous suggestions that propofol produces cardiovascular depression only in hemodynamically unstable or hypovolemic patients [12, 22]. This should be borne in mind, especially since the doses we used to induce sedation in our patients were lower that those used by other authors [12, 22, 24] or those ordinarily employed to induce anesthesia [8].

Both drugs depressed respiration, which was previously observed in dogs [26–28]. The close correlation between spontaneous minute volume and RR in the propofol individuals (Fig. 2) can result from central respiratory depression [8]. The more significant and protracted respiratory depression seen with midazolam in our study following induction may, in fact, be beneficial in the ICU. Patients newly placed on mechanical ventilation may have difficulty adjusting to the apparatus and thus "fight" the ventilator. In contrast, during maintenance and emergence, there was no difference between the groups' SIMV rate. Carrasco et al. described the respiratory effects of midazolam and propofol in humans as similar [17]. The majority of our patients in both groups could also be weaned from mechanical ventilation while still on the drug. This is the protocol we observed for weaning patients off SIMV, since we feel that it is easier to wean a calm patient off mechanical ventilation.

The issues of the advisability of producing amnesia for the duration of a patient's stay in the ICU is a complex one and beyond the scope of this paper. Admittedly, not all clinicians believe that patients should be made amnestic for their ICU stay, but there is little question that this is a legitimate and widely employed policy. It is, therefore, our policy to attempt to produce amnesia, at least for the duration of mechanical ventilation. In this respect, midazolam was superior to propofol. This is especially important, since the mean dose of propofol in our patients was 30–50 % higher than in previous studies [12].

The high rate of restlessness observed soon after discontinuation of propofol deserves further investigation. Previous publications regarding its use in the operating theater claimed no "hangover" following propofol administration [8]. At least two reports of the use of propofol for short-term sedation in the ICU documented withdrawal symptoms, including tremor, confusion, hallucination, and prolonged delusional state after its cessation [25, 29, 30].

A previous cost comparison has found the cost of midazolam to be less per patient only in a short-term sedation period [17], while another study has shown the cost of propofol to be approximately 3 times that of midazolam [31]. The present study indicates that midazolam is indeed 4–5 times cheaper than propofol for patient stay cost and per hour of use.

In conclusion, both midazolam and propofol provided equally safe and effective sedation in critically ill,

mechanically ventilated medical, posttrauma, and surgical patients for a long period of time. Both drugs allowed rapid weaning from mechanical ventilation while patients were still being sedated. Propofol was associated with more significant hypotension following induction of sedation and a lower quality of sedation and calmness both during maintenance and following discontinuation. Midazolam caused a more profound respiratory depression following induction and provided total amnesia for the duration of sedation versus partial amnesia with propofol. Midazolam costs were one-quarter to one-fifth those of propofol.

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