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Overnight sedation with midazolam or propofol in the ICU: effects on sleep quality, anxiety and depression

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Abstract *Objective:* To assess and compare the impact of overnight sedation with midazolam or propofol on anxiety and depression levels, as well as sleep quality, in non-intubated patients in intensive care.
Design: Open, comparative, prospective, randomised study.
Setting: Surgical intensive care unit (ICU) in a university hospital.
Patients: 40 conscious patients expected to stay in the ICU for at least 5 days who were admitted following trauma or elective orthopaedic, thoracic or abdominal surgery.
Measurements and results: Evaluation of a self-assessment scale (Hospital Anxiety and Depression Scale, HAD) on the day following the 1st, 3rd and 5th night of sedation with either midazolam or propofol. Heart rate, pulse oximetry and blood gases were monitored. Eight patients were excluded from the analysis. The level of anxiety was severe (HAD >10) in 31% of the patients receiving midazolam and in 26% ($p = 0.1$) receiving propofol after the first night of sedation, with no significant improvement over the next few days. The levels of depression remained high (>10) in 54% of patients receiving midazolam, and in 16% of the patients receiving propofol ($p = 0.15$). Sleep quality tended to improve during the study in the two groups.
Conclusions: These data show that half of the patients in the ICU experienced high levels of anxiety and depression during the first 5 post-operative or post-trauma days in the ICU. The beneficial effects of sedation on sleep quality were comparable for midazolam and propofol, regardless of a lack of improvement in anxiety and depression. However, an improved quality of sleep could help to re-establish a physiological night and day rhythm.

Key words Sedation · Propofol · Midazolam · Intensive care unit · Surgical · Mental disorders · Sleep disorders · Hospital Anxiety and Depression Scale

Introduction

The intensive care unit (ICU) frequently represents a hostile environment for the patient [1]. Anxiety and depression can be considered as an inevitable ultimate reaction to major stress. The discomfort caused by pain, constantly lying in a supine position, intravascular catheters and invasive procedures such as intubation and mechanical ventilation, as well as the related noise level, may heighten the depersonalising effect of the high-technology surroundings [2]. Sleep deprivation and a disturbed night and day cycle also may increase the patient's emotional distress. The disturbed sleep pattern and loss of perception and control of the situation increase the patient's stress and leads to higher levels of anxiety and depression [3]. Anxiety and depression have been investigated in patients in coronary care units [4, 5] and

in patients with life-threatening complications of haematological malignancy [6].

The aim of the present study was to analyse the level and clinical course of patient's anxiety and depression and to compare the effects of overnight sedation with midazolam and propofol on these disorders in selected patients admitted to a surgical ICU.

Patients and methods

Forty conscious, non-intubated patients between 18 and 75 years of age of both sexes, whose expected stay in the ICU was at least 5 days, were included in the study. All had a central venous and radial catheter inserted for routine monitoring. The study was submitted to and approved by the Committee on Ethics in Human Research at our institution. Exclusion criteria were any known neurological disorder, head trauma, long-term therapy with psychotropic drugs or sedatives or alcohol abuse. At admission to the ICU, informed consent was obtained and the patients were then prospectively randomised in an open fashion to receive either midazolam (bolus of 0.01–0.07 mg/kg over 2 min and subsequently a continuous infusion at a rate of 0.03–0.2 mg/kg per h) or propofol (bolus of 0.2–0.3 mg/kg over 2 min, followed by a continuous infusion at a rate of 0.3–3 mg/kg per h). The bolus was given at 10.00 p.m. on the day of admission and the continuous infusion was stopped at 6.00 a.m., for 5 consecutive nights. The infusion rate was adjusted to maintain a sedation level of 3 on the Ramsay sedation scale [7], corresponding to a sedated patient responding to commands only (assigned 3) or responding briskly to light glabellar tap (assigned 4). The maintenance of a steady sedation level was regularly checked by the nurse in charge of the patient, so that the infusion rate was adjusted accordingly. Morphine was given intravenously or provided via an extradural catheter, to assure adequate pain control in each patient (visual analogue score <3 in a scale of: 0 = no pain, 10 = worst imaginable pain). The levels of anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HAD) [8], which consists of two sets of seven questions. The first five items of the HAD evaluate the quality of sleep, the degree of restlessness, dreams or nightmares and memories about the night-time. Scores of 7 or less are considered to indicate absence of anxiety or depression, scores of 8–10 indicate doubtful cases, and scores of 11 or more indicate a definite significant anxiety or depression. Patients were asked to answer the HAD questionnaire at noon on the day following the 1st, 3rd and 5th night of sedation. They read the questions themselves and marked their answers with pencil. One of the investigators checked that all answers were filled in. The level of compliance was very good in all patients. A 2 day interval was left between questionnaires to prevent memorising of questions and answers.

During the study period, vital signs and levels of sedation were recorded hourly and arterial blood gases every 2 h.

Comparisons between treatment groups were made by non-parametric analysis (Mann-Witney U test). All tests performed were two-tailed, with a 5% probability of a type I error. The unpaired two-tailed *t*-test was used to compare demographic data and clinical parameters. A p value of <0.05 was considered statistically significant. Data are expressed as mean ± SD.

Results

Forty patients were eligible to enter the study and none refused consent. The two treatment groups, midazolam (M; $n = 20$) and propofol (P; $n = 20$), were comparable in terms of mean age (M: 41 ± 16 years, median 42 years; P: 48 ± 17, median 50), weight, height, Acute Physiology and Chronic Health Evaluation II score, analgesic treatment and costs of sedation (Table 1). No patient received other sedative benzodiazepines or psychotropic drugs during the study period.

The dose amount of administered to the M group as a bolus infusion averaged 4.0 ± 1.6 (mean ± SD) mg and the maintenance infusion 2.7 ± 0.9 mg/h. In the P group, the bolus averaged 21.4 ± 10.2 mg and the maintenance infusion 78.0 ± 54.4 mg/h (Table 1). With these doses, a Ramsay score of 3 was maintained overnight in all patients.

Table 1 Demographic data, analgesia, sedation dosage and costs. Data are expressed as mean ± SD (ranges) (*U* emergency admission, *E* elective postoperative, *SF* Swiss francs)

Variable	Midazolam ($n = 13$)	Propofol ($n = 19$)
Age (years)	41 ± 16 (18–68)	48 ± 17 (18–70)
Weight (kg)	70.1 ± 8.4 (50–82)	71.4 ± 8.2 (49–80)
Height (cm)	174 ± 7 (164–185)	171 ± 8 (160–183)
APACHE II score	14.5 ± 4.1 (9–21)	13.5 ± 4.5 (8–20)
Patient diagnosis		
Multiple injuries (U)	4	7
Abdominal surgery (U)	0	1
Thoracic surgery (E)	3	3
Abdominal surgery (E)	3	5
Orthopaedic surgery (E)	3	3
Sedation dosage		
Induction (mg)	4.0 ± 1.6 (3–8)	21.4 ± 10.2 (12–60)
Maintenance (mg/h)	2.7 ± 0.9 (2–5)	78 ± 54.4 (17–204)
Analgesic route requirements	*N*	*N*
Epidural morphine	11	17
Intravenous morphine	2	2
Costs of sedation (SF/8 h)	54 ± 18	66 ± 46

Table 2 Anxiety and depression scores and quality of sleep scale (*HAD* Hospital Anxiety and Depression Scale)

Day after admission	Midazolam					Propofol				
	HAD score (mean ± SD)	Score (%)			Range (min – max)	HAD score (mean ± SD)	Score (%)			Range (min – max)
		≥7	8–10	>10			≥7	8–10	>10	
Anxiety										
Day 1	6.7 ± 4.7	38	31	31	1.6 – 14.6	6.7 ± 3.9	42	32	26	0.6 ± 14.6
Day 3	6.5 ± 4.5	46	31	23	1.4 – 16.9	6.8 – 3.1	53	37	10	0 – 12.3
Day 5	7.5 ± 5.2	38	8	54	1.5 – 15.9	5.7 – 4.1	58	16	26	0.5 – 12.6
Depression										
Day 1	7.5 ± 5.5	38	8	54	1.5 – 15.9	5.9 ± 4.0	63	21	16	1.4 – 14.5
Day 3	6.8 ± 4.8	46	23	31	1.7 – 12.4	6.0 ± 3.0	63	26	11	0.4 – 12.0
Day 5	7.2 ± 5.1	46	16	38	1.3 – 13.7	5.5 ± 3.9	63	26	11	1.4 – 12.6
Quality of sleep (bad = 0; good = 10)										
Day 1	6.3 ± 3.4				0.7 – 9.9	6.5 ± 3.3				0.6 – 10
Day 3	6.3 ± 3.2				0.6 – 9.7	6.6 ± 2.9				0.1 – 10
Day 5	7.2 ± 2.9				0.1 – 9.7	7.2 ± 2.3				1.9 – 9.6

Seven patients in the M group were excluded during the study (age 60 ± 8 years, median 59): 5 because of paradoxical reactions (including confusion, dysphoria, and restlessness) and 2 because of premature withdrawal from the study due to discharge from the ICU. In the P group, 1 patient did not complete the study because of being in an extreme anxious state, which prevented him from answering the questionnaire. Thirty-two cases were suitable for the statistical analysis (M, $n = 13$; P, $n = 19$; Table 1). Twenty patients had had elective surgery (9 in the M group, 11 in the P group), while 12 patients (4 M, 8 P) had thoracic or abdominal trauma (11) or peritonitis (1) (Table 1).

Anxiety

After the first night of sedation, the overall level of anxiety was already severe (score >10) according to the HAD in 9/32 (28%) patients (4/13 (31%) M, 5/19 (26%) P). In the M group 4/13 (31%) and in the P group 6/19 (32%) patients had scores of borderline significance (score 8–10) (Table 2). The mean score was 6.7 ± 4.7 in the M group and 6.7 ± 3.9 in the P group on day 1 ($p = 0.97$). No significant improvement or deterioration was observed with nocturnal sedation on day 3 and day 5 in either group: the mean score was 6.5 ± 4.5 in the M group and 6.8 ± 3.1 in the P group on day 3 ($p = 0.85$); 7.5 ± 5.2 in the M group and 5.7 ± 4.1 in the P group on day 5 ($p = 0.52$; Figs. 1a, 2a).

Depression

A severe degree of depression was already present after the first night of sedation in both groups. The level of depression was abnormal (score >10) in 7/13 (54%) patients in the M group and of borderline significance in 1 patient (Table 2). Six of these 7 patients also presented a severe degree of anxiety. All patients presenting severe and borderline depressions scores in this group remained in a depressed mood during the study period, while no patient experienced a new onset of a depressive state (Fig. 1b).

In the P group, 3/19 patients (16%; $p = 0.15$, compared to patients in the M group, Fisher's exact test) had a score >10 and 4 patients had a score of borderline significance on day 1 (Table 2). Six of these patients suffered from a severe level of anxiety. During the study period, 5 patients showed a persistent depressive mood, while 2 improved following the 3rd night of sedation. Additionally, 1 patient had a high score only on day 3 and another on days 3 and 5 (Fig. 2b).

When the two groups were compared, no differences were noted either on day 1, day 3 or day 5 (score: 7.5 ± 5.5 in the M group, 5.9 ± 4.0 in the P group on day 1, $p = 0.23$; 6.8 ± 4.8 vs 6.0 ± 3.0 on day 3, $p = 0.54$; and 7.2 ± 5.1 vs 5.5 3.9 on day 5, $p = 0.12$).

Sleep quality tended to improve during the study, mainly for the last night of sedation, but the change did not reach statistical significance. No significant difference

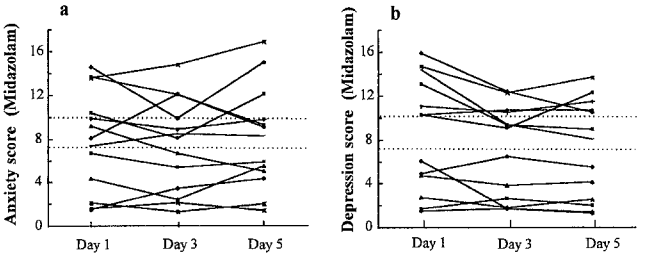

Fig. 1 Patient anxiety **a** and depression **b** scores, as assessed during the day by the Hospital Anxiety and Depression Scale, after the 1st, 3rd and 5th night of sedation, in 13 patients sedated overnight with midazolam during the ICU stay. *Dotted lines* indicate the interval scores of borderline significance

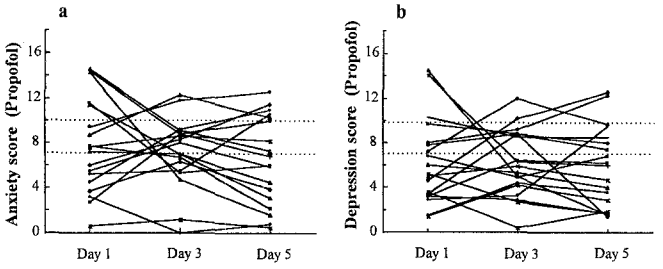

Fig. 2 Patient anxiety **a** and depression **b** scores, as assessed during the day by the Hospital Anxiety and Depression Scale, after the 1st, 3rd, and 5th night of sedation, in 19 patients sedated overnight with propofol during the ICU stay. *Dotted lines* indicate the interval scores of borderline significance

in sleep quality was observed between the two types of treatment (Table 2).

The clinical parameters analysed, including heart rate, oxygen saturation and partial pressure of carbon dioxide in arterial blood ($PaCO_2$), showed no statistically or clinically significant changes between day-time and night-time sleep; in particular, overall mean $PaCO_2$ increased by 0.4 kPa in the P group and by 0.1 kPa in the M group during sedation, compared to mean daily values (changes not statistically significant).

Discussion

In the present study, we assessed anxiety and depression levels after the 1st, 3rd, and 5th night of sedation during the ICU stay in patients sedated overnight with either propofol or midazolam. Levels of anxiety and depression, as measured by the HAD, were comparable between the two groups. Interestingly, in both groups about 50% of the patients had increased anxiety and depression scores and a third had a definitely pathological score (>10 on the HAD) which remained at abnormal levels during the observation. The quality of sleep was similar in both groups and showed a tendency to improve with time. Midazolam and propofol were chosen for sedation and sleep induction because they are the most widely used sedative drugs in surgical ICUs [9, 10]. Both agents are suitable in this context, showing no major interactions or side-effects [11]. However, in our study, there were more drop-outs in the midazolam group, due to the paradoxical effects produced by this drug.

The HAD has been used to assess patients suffering from major depressive episodes as well as physically ill hospitalised patients [12, 13], allowing the severity of these mood disorders to be measured, and therefore its repeated use can provide useful information. The HAD has so far had limited application in the ICU setting; however, a recent study performed in a coronary care unit and comparing three different scales (State-Trait Anxiety Inventory, HAD and Linear Analogue Anxiety Scale) showed that the HAD has the highest test-retest reliability [14]. The consistency of the HAD with standard scales such as the Hamilton Rating Scale for Depression and Anxiety or the Montgomery and Asberg Depression Rating Scale is well established [15].

To date, anxiety has been investigated mainly in medical ICUs, particularly in patients with heart disease [16, 17]. The reported incidence of mental disturbances in coronary care patients varies widely, i.e. between 10 and 50% [18, 19]. We found that half of our patients presented abnormal levels of anxiety. It is important to control anxiety in the ICU since it heightens the stress response [20], which in turn increases oxygen consumption, water and sodium retention and catabolism, and decreases the immune response [21, 22]. Early diagnosis of anxiety disorders would improve patient management in the ICU and during subsequent rehabilitation.

The incidence of depression in ICU patients is not well known. Using the HAD, we found a high incidence of depression, i.e. 31% of the patients studied. Clarification of misconceptions, help in understanding and anticipating events that are part of the illness, as well as encouraging an optimistic outlook, may help to reassure the patient. Explanation and reassurance by the medical and nursing team can have a therapeutic effect and reduce the need for drug use [23, 24].

Alterations in sleep patterns are common in ICU patients and recognised as one of the main causes of anxiety [25, 26]. Abnormal sleep patterns are associated with disorientation, psychological disturbances and fatigue, which also contribute to the increased stress response and may lead to delayed weaning from the ventilator. Some authors suggest that the restoration of normal sleep patterns results in a lowered mortality and less need for concomitant drugs [27, 28]. Sleep deprivation also affects the respiratory and immune systems [29]: forced vital capacity, maximum voluntary ventilation, hypercapnic and hypoxic ventilatory responses are decreased [30, 31]. We observed that in contrast to the anxiety and depression levels, the quality of sleep had a tendency to improve during the study. We believe that this improvement is due to both a progressive decrease of postoperative or post-traumatic pain and appropriate overnight sedation.

A possible bias in this study may be due to the different pharmacokinetics profiles of the two study drugs. As infusions were terminated 6 h prior to mood testing, a post-drug effect could have affected the choice of answers differently. Indeed, depressed mood is one of the after-effects of benzodiazepines. However, in this study, sedation was administered with the aim of restoring the night and day cycle and preventing sleep deprivation, which may influence the subjective appreciation of the quality of the ICU stay. Furthermore, the present study was not double-blind, but again drugs have different characteristics and features, and problems with dose ad-

justment would have occurred with a potential risk of oversedation. For this reason standardisation was obtained by maintaining a comparable level of sedation, i.e. Ramsay 3. Hence, the design of the study does not include a placebo group to test for the inability to obtain constant overnight sedation at a Ramsay score of 3. Before starting sedation, a baseline assessment was not carried out because patients were admitted either in emergency or elective conditions and sedation was started the night of admission.

In conclusion, the present study shows that the levels of anxiety and depression assessed by the HAD are high in the first 5 postoperative or post-trauma days in the ICU. Half of the population studied presented severe levels of anxiety and depression. Overnight sedation with midazolam or propofol to prevent sleep deprivation in the ICU does not seem to affect significantly anxiety or depression after trauma or major surgery. However, the role of these drugs in improving the quality of sleep and in re-establishing a physiological night and day cycle needs to be elucidated.

Medical and nursing staff must be aware of these common psychological disturbances, which reduce the quality of the ICU stay for conscious patients, in addition to other organ dysfunctions. Further efforts are needed to improve the control of anxiety and depression in the first post-operative or post-trauma days.

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