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CRITICAL CARE

A comparison of hypnotic and analgesic based sedation in a general intensive care unit†

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Background. Sedation of the critically ill patient has several components including hypnosis and analgesia. Hypnotic-based sedation (HBS), where midazolam and/or propofol are used, with morphine or another analgesic added as needed has been common. The advent of remifentanil has allowed greater use of analgesia-based sedation (ABS) where relief of discomfort from the tracheal tube or pain are the important objectives, and hypnosis is given as necessary.

Method. We compared HBS and ABS (remifentanil-based sedation) within a general intensive care unit (ICU). During the first study period of 12 weeks, 111 patients received HBS. After the development of new guidelines for the use of remifentanil in the ICU, a second 12 week study period used an analgesia-based regimen, with hypnotics added only if needed.

Results. Ninety-six patients received ABS, and 79 received remifentanil. It was possible to manage 29 (37%) of the patients receiving remifentanil without the use of supplementary hypnotic agents. In the remaining 63% the use of remifentanil was associated with a reduction in the amount and duration of propofol used. Significantly more patients receiving ABS had satisfactory levels of sedation during synchronized intermittent mandatory ventilation (19 [2,55] *vs* 50 [14,83], $P<0.001$).

Conclusions. The use of ABS allowed patients to be managed more comfortably, either without a hypnotic drug or with less hypnotic drug, than using conventional HBS.

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Critically ill patients are often uncomfortable in the intensive care unit (ICU). This may be attributable to painful or distressing procedures; they may also find the environment frightening, and the constant noise can make sleep difficult. A further reason for patient discomfort and distress is the presence of a tracheal tube and mechanical ventilation.

Various ways to deal with patient discomfort have been developed. Analgesic drugs, such as morphine were unpredictable, especially in patients with multiple-organ failure,[1] but in the late 1980s and early 1990s, the development of predictable hypnotic drugs, such as midazolam and propofol, led to hypnotic-based sedation (HBS) becoming a common approach.[2 3] With this technique the hypnotic component is titrated to a level of consciousness thought desirable by the ICU staff and analgesia often given as they think appropriate. Sedation with these agents means that patients do not complain of pain, but patient discomfort and pain are difficult to assess in unconscious patients.[4]

In 1996, remifentanil, a potent selective μ opioid receptor agonist, was licensed as an analgesic agent for use during induction and/or maintenance of general anaesthesia. The unique properties of remifentanil, with its metabolism by non-specific esterases found in the plasma and tissues, result in rapid and predictable clearance independent of renal and hepatic function. The antitussive and analgesic effects of a non-cumulative high dose opioid technique are particularly

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attractive.[5] Hypnosis is only added if the patient needs it (analgesia-based sedation, ABS). Because the patient is awake analgesia and hypnosis can be titrated to the patients expressed needs, unlike HBS when these are titrated to the needs perceived by the patients' attendants.

It was not until 2002 that remifentanil became licensed for use in the critically ill. Early data from registration studies for remifentanil indicated that analgesia and patient comfort were achieved without the need for supplementary hypnotic agents in around 70% of ICU patients.[6 7] The aim of this study was therefore to compare hypnotic- and analgesia (remifentanil)-based sedation outside of a research setting, within a general ICU and to see if the amount of hypnotic agent used could be reduced, along with the length of mechanical ventilation.

Methods

After Ethics Committee approval, we studied the influence of HBS or ABS approaches over a 12-week period. During the first 12 week study period (February 18, 2002–May 12, 2002), a 'conventional' hypnotic-based regimen was used, with hypnotic agents being the major component of the sedative regimen and morphine added as required for analgesia. The protocol in use for the first 12 weeks is shown in Figure 1.

Over the next 2 months, guidelines were developed for the use of remifentanil in the critically ill based on the available literature;[6 7] the primary aim was to relieve pain, with a hypnotic agent given only if required to achieve patient comfort (Fig. 2). During this time, we educated the nursing and medical staff on the use of remifentanil and the study protocol. Only small amounts of remifentanil had been used in the ICU before this study.[8]

In the second 12 week study period (July 29, 2002–October 20, 2002), remifentanil was used as the principal agent for the control of pain and ventilator asynchrony; with hypnotic agent supplementation if required. Patients receiving neuromuscular blocking agents were excluded from the remifentanil protocol because of concerns that they could be awake and paralysed if the drug was used incorrectly. Similarly, at that time, we were not sufficiently confident to use the drug in patients with encephalopathy.

In many patients, both midazolam and propofol were used, especially in the early stages of admission when anaesthesia may be induced to facilitate tracheal intubation and starting mechanical ventilation. Hypnosis was considered to be mainly with propofol if more than 1000 mg was given or with midazolam if more than 10 mg was used during the whole of the ICU stay (excluding any drugs used during anaesthesia). In the ABS group, patients were classed as receiving remifentanil alone if the doses of hypnotic agents were <1000 mg propofol or 10 mg midazolam during the whole of the ICU stay (excluding any drugs used during anaesthesia).

During both study periods, basic demographic data were collected including age, gender, diagnosis and APACHE II score[9] for every patient. Every hour, any drugs administered for hypnosis and analgesia, and their dosage, were recorded. The effects of these drugs were routinely recorded every hour using our own sedation scale,[10] which not only assessed the level of consciousness on a seven-point scale, but also whether the patient was in pain and if they were tolerating the ventilator.

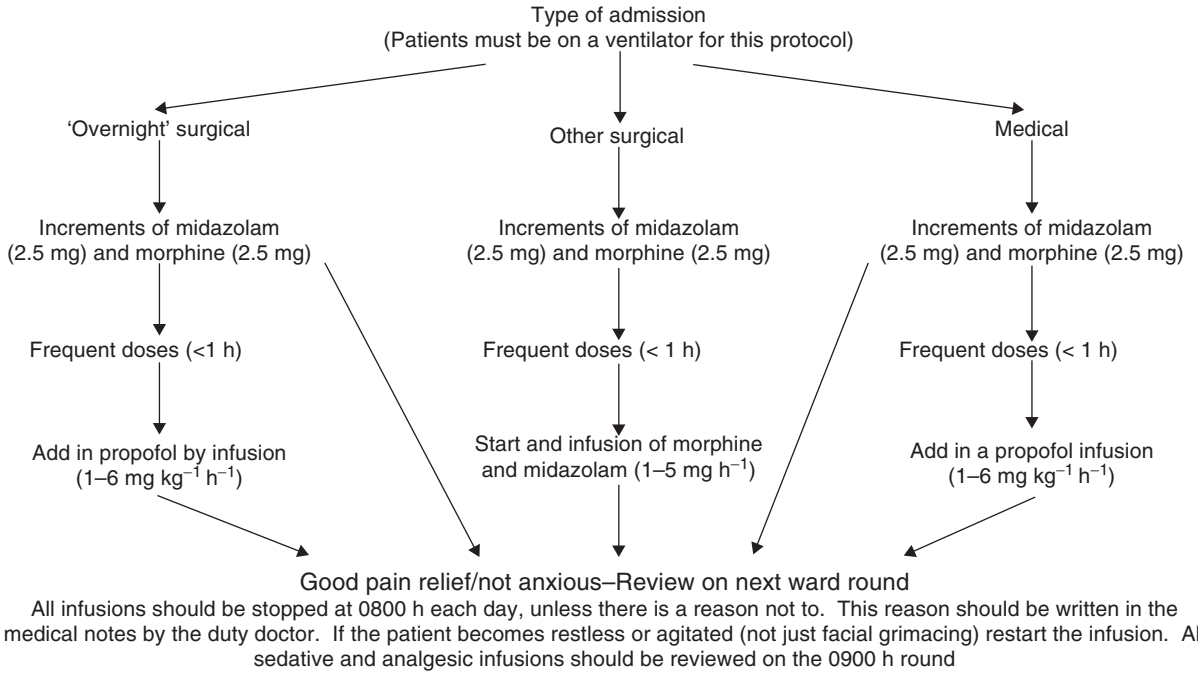

Fig 1 Hypnotic-based sedation and analgesia in the first 24 h after ICU admission.

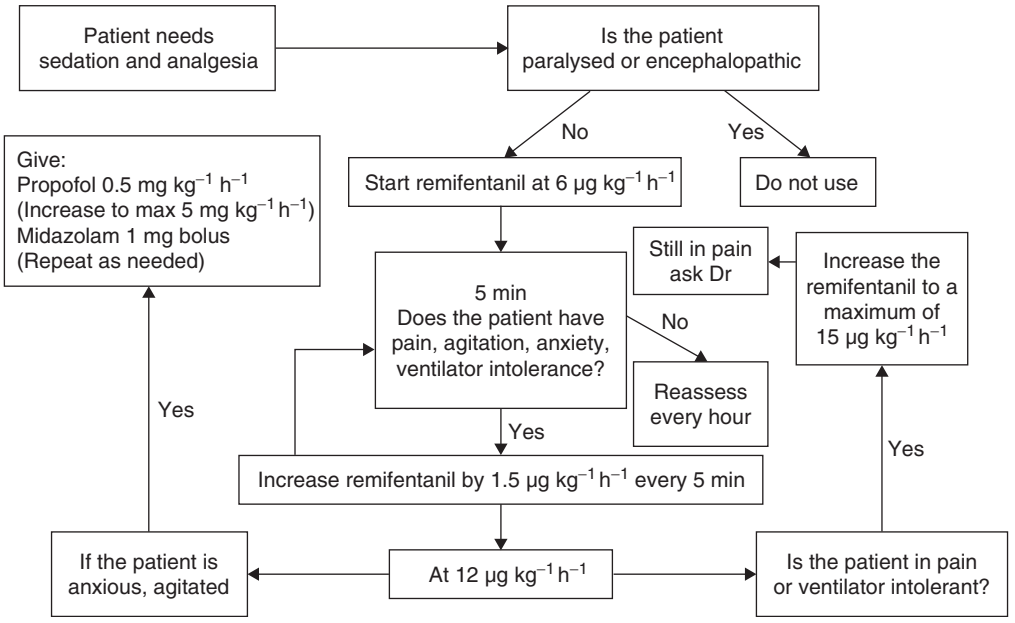

Fig 2 Protocol used to give remifentanil during the second study period.

As the use of these hypnotic agents may also affect the period of mechanical ventilation,[11–13] the mode of ventilation was recorded every hour allowing calculation of the amount of time spent attached to a mechanical ventilator, as well as the time spent on individual modes of mechanical ventilation. Similarly, the need for ventilatory support determines the need for sedation, especially hypnosis. We therefore recorded the times when patients received support modes that were considered indicators of pulmonary dysfunction: synchronized intermittent mandatory ventilation (SIMV), biphasic airway pressure (BIPAP) and intermittent positive pressure ventilation (IPPV) and pressure supported breathing (PSB). We considered that patients who were breathing spontaneously or just with continuous positive airway pressures were not receiving ventilatory support. We divided the ventilatory support types into those indicating significant respiratory support (SIMV, IPPV and BIPAP) and predominately weaning (PSB). As BIPAP and IPPV were not commonly used within our unit at that time, we called the group getting significant respiratory support SIMV.

Dreaming, nightmares and hallucinations are common in the critically ill and have many causes. These may lead to serious adverse psychological sequelae, such as post-traumatic stress disorder. The type of sedation and analgesia used to make patients comfortable may influence this. As part of follow-up in the first 4 days after discharge, all patients are asked whether they had any dreams, nightmares or hallucinations and, if so, were they distressing? They were also asked about pain on transfer.[14] In addition, a sample of 15 patients, who received remifentanil only (no routine hypnotic) in the second period of the study, were visited to ask about pain and general satisfaction with the technique.

Data were entered into a Microsoft Access Database (2000), which was used for analysis. The main aim of the statistical analysis was to compare the results between the two study periods. For each outcome variable, two comparisons were performed: firstly, the difference between all subjects receiving hypnotic-based therapy and all subjects receiving analgesia-based therapy.

The patient demographic and clinical characteristics of the groups were compared. Those variables measured on a categorical scale were compared between groups using the χ^2-test. Normally distributed continuous variables were compared between groups using the two-sample *t*-test, whilst continuous variables that were not distributed normally were compared between groups using the Mann–Whitney test.

For each subject, three measures relating to drug administration were calculated. The first measure was whether or not each subject received the drug at any stage during the study. Fisher's Exact test was used to compare the number of subjects who received each drug in each of the study periods. In addition, for those subjects who received a drug, the amount of time that the drug was received and the mean dose were calculated; infusion and bolus drug doses were treated separately for the purposes of analysis. The time each drug was given was compared between groups using the Mann–Whitney test, as the measures of time received were not normally distributed. The distributions of the mean drug doses were found to be approximately normally distributed, and so the two-sample *t*-test was used to compare these data.

Outcome measures for the type of ventilation used and the satisfaction of the sedation were calculated for each subject, based on the results recorded at hourly intervals.

All calculated variables were measured on a continuous scale, and were not normally distributed. Differences in the outcomes between groups were therefore examined using the Mann–Whitney test. Separate analyses were performed for SIMV only, PSB only, and also for a combination of SIMV and PSB.

Results

A total of 134 patients were initially assigned to receive HBS; of these, 23 were excluded from the analysis—21 did not receive invasive mechanical ventilation and 2 had encephalopathy. Of the remaining 111 patients, 61 received mainly propofol and 21 mainly midazolam, while 25 received a mixture of both. As well as the hypnotic agents, morphine was given to all patients. Of the remaining four patients, two patients died almost immediately on admission, one was given morphine and one fentanyl only.

During the second study period, 141 patients were evaluated to see if they could receive ABS. Invasive mechanical ventilation was not used in 43 patients and two were encephalopathic, thus excluding 45 patients from the analysis. Twenty-nine patients were given remifentanil only, while 27 patients received additional propofol, 10 additional midazolam and 13 a mixture of both hypnotics as well as remifentanil giving a total of 79 patients receiving remifentanil. Of the remaining 17 patients, 2 died almost immediately on admission to the ICU; in 15 patients, a consultant decided not to use remifentanil (one patient each received propofol, midazolam, propofol and midazolam, midazolam and morphine, while seven received propofol and morphine, two morphine and midazolam and two propofol, midazolam and morphine). Data are shown throughout with the HBS followed by the PSB result (Table 1).

The demographics and the clinical characteristics of the patients recruited over the two study periods are summarized in Tables 1 and 2, respectively. There was no significant difference between the hypnotic and analgesia groups for any of the characteristics recorded.

There was a significant reduction in the numbers of patients receiving propofol by infusion in the ABS groups during the times they received different modes of ventilatory support: SIMV [*n*(%) 95 (86) *vs* 67 (70), $P<0.01$), PSB [58 (52) *vs* 22 (23), $P<0.001$] and SIMV/PSB combined [95 (86) *vs* 67 (70), $P<0.01$].

Table 1 Patient characteristics: hypnotic-based therapy

	Hypnotic-based therapy				
	Propofol	**Midazolam**	**Mixture**	**Others**	**All patients**
Number	61	21	25	4	111
Age (yr), mean (range)	60.1 (17–94)	64.7 (17–94)	51.3 (17–94)	51.0 (17–94)	58.7 (17–94)
Males, *n* (%)	41 (67)	12 (57)	17 (68)	1 (25)	71 (64)
APACHE II, mean (SD)	14.7 (6.1)	19.9 (11.1)	18.5 (5.4)	12.5 (10.4)	16.5 (7.6)
ICU mortality, *n* (%)	10 (16)	7 (33)	6 (24)	3 (75)	26 (23)
Hospital mortality, *n* (%)	12 (20)	10 (48)	6 (24)	3 (75)	31 (28)
Elective surgical, *n* (%)	8 (13)	1 (5)	1 (4)	0	10 (9)
Emergency surgical, *n* (%)	31 (51)	9 (43)	9 (36)	1 (25)	50 (45)
Medical, *n* (%)	22 (36)	15 (52)	15 (60)	3 (75)	51 (46)
Total time needing mechanical ventilation (h), median (IQ range)	21 (14,59)	33 (22,135)	291 (134,451)	2 (1,25)	37 (16,138)
Length of stay in ICU (h), median (IQ range)	47 (29,116)	69 (24,156)	315 (161,564)	12 (1,29)	67 (31,258)

Table 2 Patient characteristics: analgesia-based therapy

	Analgesia-based therapy						**Hypnotic *vs* analgesia *P*-value**	**Hypnotic *vs* remifentanil *P*-value**
	Remifentanil	**Remifentanil +propofol**	**Remifentanil +midazolam**	**Remifentanil +mixture**	**Others**	**All patients**		
Number	29	27	10	13	17	96		
Age (yr), mean (range)	60.8 (19–89)	56.7 (19–89)	50.4 (19–89)	58.7 (19–89)	52.6 (19–89)	56.8 (19–89)	0.48	0.58
Males, *n* (%)	14 (48)	18 (67)	9 (90)	7 (54)	7 (41)	55 (28)	0.33	0.12
APACHE II mean (SD)	17.9 (6.7)	15.0 (8.8)	19.8 (3.8)	24.5 (12.3)	17.6 (10.1)	18.1 (9.0)	0.15	0.34
ICU mortality, *n* (%)	4 (14)	4 (15)	4 (40)	6 (46)	7 (41)	25 (26))	0.67	0.26
Hospital mortality, *n* (%)	6 (21)	9 (33)	5 (50)	6 (46)	8 (47)	34 (35)	0.48	0.29
Elective surgical, *n* (%)	3 (10)	1 (4)	1 (10)	0	2 (12)	7 (7)		
Emergency surgical, *n* (%)	19 (66)	10 (37)	4 (40)	3 (23)	6 (35)	42 (44)		
Medical, *n* (%)	7 (24)	16 (59)	5 (50)	10 (77)	9 (53)	47 (49)		
Total time attached to ventilator (h), median (IQ range)	18 (12, 73)	83 (17, 210)	206 (89, 309)	329 (205, 554)	19 (9, 78)	71 (16, 226)	0.37	0.07
Length of stay ICU (h), median (IQ range)	47 (23, 125)	175 (28, 227)	217 (93, 395)	373 (236, 635)	26 (13, 127)	118 (26, 255)	0.46	0.09

During SIMV, there was a significant difference in the number of subjects receiving midazolam by infusion. In the HBS group 44 (40%) subjects received midazolam, compared with only 15 (15%) in the ABS group ($P<0.001$).

As might be expected, significantly more patients receiving HBS required additional analgesia in the form of morphine boluses [29 (26%) *vs* 6 (6%), $P<0.001$]. On comparing the length of time that each drug was given showed that the HBS group received propofol for a longer time than the ABS group when they were receiving SIMV (median [IQ range] 13 [8,25] *vs* 4 [2,8] h, $P<0.001$) and when SIMV and PSB were combined (20 [12,54] *vs* 4 [3,8] h, $P<0.01$). Conversely, the duration that the bolus doses of midazolam were used was reduced when HBS was used during the whole time of mechanical ventilation (4 [1,83] *vs* 9 [3,15] h, $P<0.05$).

As with the duration of drug administration there were significant differences in the mean (SD) doses of propofol used between the HBS and ABS groups during SIMV [170 (91) *vs* 126 (67) mg h^{-1}, $P<0.001$] and during SIMV/PSB [157 (87) *vs* 122 (63) mg h^{-1}, $P<0.01$]. No significant differences were found during PSB, when, as expected, all doses were generally lower reflecting weaning from ventilation and reduced pain and discomfort.

Time on SIMV as a percentage of the total time on mechanical ventilation was less for the HBS patients (median [IQ] h) (78 [56,94] *vs* 86 [60,100]), but this did not achieve statistical significance ($P<0.09$). However, time on PSB as a percentage of the total time on ventilator was significantly greater for the HBS than the ABS group (22 [5,40] *vs* 9 [0,35], $P<0.01$). This difference may reflect a reduced weaning time with ABS therapy.

We defined satisfactory sedation as being awake or easily rousable. The use of ABS was associated with a greater percentage of time at a satisfactory sedation level, irrespective of the addition or not of a hypnotic agent when SIMV was used (median [IQ range]) (19 [2,55] *vs* 50 [14,83], $P<0.001$), and during PSB when remifentanil was used alone (88 [45,100] *vs* 100 [92,10], $P<0.01$). There was no other significant difference overall between the HBS and ABS groups during PSB.

Other observations

At first it appeared that there were more instances of accidental self extubation in the ABS patients, a potential hazard with less sedated patients. However, analysis of these events in the ABS group revealed that two patients were not on remifentanil. Two were receiving remifentanil+propofol and one remifentanil alone. There were two accidental self extubations in the HBS-based group, one patient was on a propofol infusion and the second receiving bolus doses of midazolam. All of the self extubations in both groups were re-intubated immediately, although the three patients receiving remifentanil were all successfully extubated within the following 12 h, perhaps indicating that re-intubation was unnecessary in some.

Throughout the second study period, atracurium was given to a number of patients given remifentanil, despite this being an exclusion criterion. A significant dose was considered to be more than 100 mg; this allowed for paralysis to facilitate tracheal intubation and for procedures such as percutaneous tracheostomy, neither of which should have affected long-term sedation. On each occasion, the protocol violation was discussed with the consultant involved (all of whom were anaesthetists) who decided to continue with the remifentanil. No neuromuscular blocking agent was used in patients given remifentanil alone, but it was given to seven patients receiving remifentanil in combination with hypnotics (three patients who were given propofol, one given midazolam and three who received both hypnotics), as well as in two of the 17 patients not given remifentanil.

Follow-up

Following the first study period (HBS), 47 patients were followed up and 20 (42%) of them experienced dreams or hallucinations, with 13 (65%) finding the experience distressing. In the second study period (ABS), 57 patients were seen and 28 (49%) experienced dreams or hallucinations with 16 patients (57%) finding them unpleasant or distressing. Interestingly, two patients who suffered from distressing dreams/hallucinations had received no sedative or analgesic drugs, and presumably the distressing dream/hallucination was a consequence of their illness. In the sample of 15 patients receiving remifentanil alone who were specifically asked about pain, none reported pain associated with their ICU stay. Only one patient reported dreaming and this was pleasant. A further patient did not like being awake because they were bored.

Discussion

The aim of this study was to assess the use of remifentanil as part of an analgesic-based approach to see if it was possible to reduce the amount of hypnotic agents used and have more critically ill patients awake in a general ICU. In the past, improvements in ventilator technology have been associated with decreased sedative requirements, whilst patients' analgesic needs remain unchanged.[15]

The most important findings in our study was that 37% of patients given remifentanil could be managed without any hypnotic agent. In addition, in the remainder significantly more patients receiving remifentanil with an hypnotic agent had satisfactory levels of sedation (awake or easily arousable) during SIMV compared with those receiving hypnotic-based therapy. During PSB the incidence of satisfactory sedation was higher in all groups, but remained statistically higher for those patients receiving remifentanil alone compared with the hypnotic-based therapy group. Furthermore,

significantly fewer patients in the analgesic-based therapy group required a propofol or midazolam infusion during SIMV or SIMV/PSB combined and significantly fewer required propofol infusion during PSB compared with the patients receiving HBS.

In studies, the use of hypnotic agents was avoided in 65–78% of patients when remifentanil was given first to provide analgesia and patient comfort.[6 7] In our study, we took almost all those who come to the ICU; it was possible to manage 29 of the 79 patients (37%) receiving remifentanil without the use of supplementary hypnotic agents [29/141 (21%) when considering the intention to treat population]. This difference reflects routine working practices rather than research study in our patients. Keeping patients awake is more difficult for the nursing staff (especially the less experienced nurses—data not shown) who may find it easier to manage patients who are unconscious rather than awake.

Bolus doses of midazolam were used for a shorter time in the patients given HBS This may reflect the greater use of propofol by infusion. Alternatively, the patients given ABS may just have needed small infrequent doses of a hypnotic/anxiolytic as and when needed over a long time.

The advantages of keeping patients more awake have not been the subject of much research. Having patients who are awake or easily aroused can allow easier assessment of pain (by asking the patient), better patient contact with staff and family, and cooperation in procedures such as physiotherapy or neurological assessments.[4 16] The patients who were managed without hypnotic agents were unanimous about the lack of pain. However, when an analgesic-based regimen is first instituted, some staff may feel uncomfortable when patients are awake and may prefer to have them unconscious.

A potential disadvantage of being awake is increased psychological stress. We could find no evidence of this. The rate of 'dreaming' was the same in the HBS and PSB patients. The only patient who was awake and reported any form of distress was bored and would have preferred to be asleep when asked. Drugs such as propofol and midazolam have potentially dangerous adverse effects and using them to treat boredom is inappropriate. Being more awake may reduce psychological stress by facilitating factual memory and so reducing the potential for post-traumatic stress disorder.[17]

A further potential disadvantage is the risk of accidental tracheal extubation in the awake patient. At first we thought that this had happened, but investigation showed a difference in the two periods, but only one of the ASB patients was receiving no hypnotic agent. It is possible that the two other patients receiving remifentanil and a hypnotic agent were more awake than other patients receiving a conventional HBS, but these data are unavailable. The common feature to all three patients receiving remifentanil was that they were all re-intubated immediately, but successfully extubated in the next 12 h. This may be a reflection of the non-anaesthetic staffing of our ICU at the junior level and anxiety about watching a recent, unintentional extubation.

A further aim of this study was to see if the use of remifentanil changed the amount of ventilatory support patients needed. There was a trend towards less time on more invasive ventilator modes with the HBS patients. However, there was a significant reduction in time spent on PSB in patients given ABS. This suggests that there was a more rapid weaning process from mechanical ventilation. This observation has been made in a number of randomized controlled studies, where the rapid offset of effect with remifentanil has allowed more rapid weaning.[18–20]

Although adequate analgesia is widely recognized as the first need for critically ill patients, regrettably it is not always the case in clinical practice. In one Italian study, almost 50% of patients failed to receive any opioids in the first 48 h after major surgery.[21] In a further study, pain was the commonest cause of failure to sleep and when analgesia was given it was often insufficient.[22] When we used remifentanil no patient had pain and there were other significant advantages.

The question many will ask is can the same outcomes be achieved with a less expensive opioid? Using remifentanil even at its staring dose of 6 $\mu g\ kg^{-1}\ min^{-1}$ is the equivalent of a large dose of morphine that cannot be given hour after hour to the critically ill without significant risk of accumulation. Morphine has highly active metabolites that can accumulate in renal failure.[1 23] The same is true of the newer synthetic opioids that may also accumulate with prolonged use. These opioids, such as fentanyl, are nearly all metabolized by cytochrome P450 3A4, an enzyme known to have reduced function in critical illness. The reduced function of this enzyme can mean that these drugs may act for a much longer duration than expected.[1 24] If opioids act for longer than expected, then coma and respiratory depression may prolong mechanical ventilation and a failure to cough after tracheal extubation may result in the need for re-intubation of the trachea. This may explain why we have not used ABS to any significant extent in the past. Unlike other opioids, the metabolism of remifentanil is independent of liver function,[25] and although it does have an active metabolite it is so weak that even in severe renal failure it does not exert any opioid effects.[26]

In our comparison of hypnotic- and an analgesic-based sedation in a general ICU, we found that an analgesic-based approach using remifentanil achieved a satisfactory level of sedation in significantly more patients than the hypnotic-based approach, especially in patients requiring significant respiratory support.

Of those patients receiving remifentanil, 37% did not require supplementary hypnotic agents, and there was also a lower requirement for hypnotics (sedative-sparing) across the analgesic-based sedation group irrespective of the mode of ventilation. Remifentanil also provided a more satisfactory sedation level and allowed patients to be awake or easily

arousable during mechanical ventilation, allowing greater interaction with the patient and making assessments easier.

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