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Optimizing sedative use in the intensive care unit

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Introduction

Sedatives and analgesics are commonly employed in the modern intensive care unit (ICU) for the relief of patient discomfort and anxiety, for amnesia, and the provision of adequate analgesia [1]. Additionally they may be used to reduce respiratory muscle oxygen requirements in severe hypoxemic respiratory failure and to reduce patient-ventilator asynchrony. The most commonly used classes of medications for anxiolysis and relief of agitation are the benzodiazepines [2]. Butyrophenones such as haloperidol and the nonanalgesic sedative propofol are also used for this purpose. Opiates remain the usual drug of choice for analgesia. Frequently these medications are used in combination. Each may be given by continuous intravenous infusion or by intermittent intravenous boluses.

Because of the frequent use of these medications and because of the wide choice of medications, combinations of medications, and methods of administration available to the clinician, as well as the complications of overmedication, this is an important area of research in the ICU. Although a review of this topic was published in *Intensive Care Medicine* less than 2 years ago [3], a number of important studies on this topic have been published since then. This contribution reviews and discusses three of them.

Brook AD, Ahrens TS, Schaiff R, Prentice D, Sherman G, Shannon W, Kollef MH (1999) Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 27:2609–2615

This is a single-center nonblinded randomized controlled trial comparing the use of a nursing-implemented protocol for the management of sedation with usual sedation care in patients requiring mechanical ventilation. Brook and colleagues studied 332 consecutive adult medical patients in a tertiary ICU over a 12-month period. Patients were randomized at the time of initiation of mechanical ventilation. Those assigned to the intervention group were managed by means of a protocol in which nurses titrated the amount and mode of administration (intravenous bolus vs. continuous infusion) of sedative and analgesic agents according to the patient's level of sedation as measured by the Ramsay scale [4]. Benzodiazepines (diazepam, midazolam, or lorazepam) were used for sedation and opiates (morphine or fentanyl) were used for analgesia. According to the protocol the patient's sedation level was reassessed every 4 h, and either the infusion rate was turned down if the level was adequate, or the patient was rebolused if it was inadequate. In the control group all decisions regarding the patients' sedation were made by the ICU medical team. Patients were followed until hospital discharge.

The primary outcome was the duration of mechanical ventilation, and secondary outcomes included ICU and hospital length of stay, hospital mortality, reintubation rate, and tracheostomy rate. The authors performed an intention to treat analysis, and, importantly, controlled for important cointerventions by the use of a weaning protocol implemented by nurses and respiratory therapists for all patients. Their main result is that the mean duration of mechanical ventilation in the patients in the intervention group was significantly shorter, by 1.5 days, than in the usual care group. They also demonstrated a

reduction in hospital stay (5.7 vs. 6.5 days; p=0.013) and ICU length of stay (14.0 vs. 19.9 days; p<0.001), a reduced duration of continuous sedative infusions, and a lower tracheostomy rate, all statistically significant and in favor of the treatment group. There was no significant difference in either the mortality rate or the reintubation rate.

This study is methodologically generally sound. Randomization was largely successful, but the patients in the control group did have a lower incidence of congestive heart failure and a higher incidence of pneumonia. This baseline difference may have tended to increase the duration of mechanical ventilation in the control group. Recognizing that blinding is very difficult with this type of study, the lack of blinding may have resulted in bias favoring the treatment group. That is, physicians making sedation decisions (or nurses making suggestions) for the control group may not have been as aggressive with weaning sedation in the control group as they might have been under usual circumstances. The performance of this study in a single center with previous experience in sedation research [5] raises the issue of generalizability. Although the protocol is well outlined in the paper, there appear to be a large number of subjective decisions required in its implementation. We are not told whether the nurses had additional training before starting the trial, and it is unclear whether this protocol could be reproduced in other ICUs where nurses were not involved in its development. A recent paper has shown that adherence to sedation protocols outside the setting of a trial may only be moderate, and it seems clear that the degree of adherence will affect any protocol's efficacy [6]. Additionally, this study examined only medical ICU patients, and thus the applicability of this protocol to surgical patients is unknown.

Kress JP, Pohlman AS, O'Connor MF, Hall JB (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 342:1471–1477

This is a single-center randomized-controlled trial that enrolled mechanically ventilated patients who were deemed to require continuous intravenous sedation. Patients randomized to the intervention group had their sedative infusion interrupted on a daily basis starting 48 h after enrollment. While the sedation was being held, the patients were observed closely by a research nurse who then contacted a study physician when the patient either awakened or became agitated. The physician then decided whether to resume the sedative infusion, and if so, it was restarted at half of the previous rate and retitrated to achieve sedation at a Ramsay score of 3–4 [4]. The control group was managed by the ICU team in a usual care fashion. All patients in this study received morphine for analgesia, and in a factorial design they were randomized to receive either propofol or midazolam for sedation. The authors studied 128 patients in the medical ICU, excluding patients who were pregnant, those transferred from another institution where sedatives had already been started, and those admitted following a cardiac arrest. Patients were followed until hospital discharge, and an intention to treat analysis was used.

There were three primary endpoints in this study: (a) the duration of mechanical ventilation, (b) ICU length of stay, and (c) hospital length of stay. Secondary outcomes included the total doses of the medications administered, the use of neurological tests, reintubation rates, tracheostomy rates, and adverse events such as unplanned extubation and in-hospital mortality. Their main results were a reduction in the duration of mechanical ventilation in the treatment group (median 4.9 vs. 7.3 days, p=0.004) and an accompanying decrease in lengths of stay in the ICU (median 6.4 vs. 9.9 days, p=0.02) and in hospital (median 13.3 vs. 16.9, p=0.19). The mortality rate, tracheostomy rate, and reintubation rates were not different between the groups; however, the control group did have more neurological tests ordered. When comparing patients randomized to propofol vs. midazolam, there were no significant differences in any of the primary endpoints.

The groups were randomized and appeared to be equal at baseline. We are not told whether the patients were consecutive, nor is any information given about how it was decided that patients needed continuous intravenous infusions of sedatives. Out of necessity healthcare personnel were not blinded to treatment assignment in this study. The main concern with the internal validity of this trial, however, lies in the area of cointerventions. A standardized ventilator weaning protocol was not used, and no details regarding weaning are provided. This, along with the lack of blinding, raises the possibility that bias may have been inadvertently introduced if the intervention patients were weaned from the ventilator more aggressively than those in the control group. This would tend to diminish the demonstrated effect size to some degree.

The other issue with this trial is its generalizability. While the intervention in this trial may be technically easier to reproduce than the sedation protocol used in the Brook et al. study, it is also significantly more demanding in terms of human resources. A dedicated nurse who observed the patient for signs of awakening or agitation was present whenever the infusions were stopped in the intervention group. The safety and efficacy of this protocol in the average ICU where many additional demands are placed upon nurses' time are unclear. One final concern with this protocol's applicability is the effect it may have on patient comfort. Patients surviving their ICU stay often have reduced health-related quality of life, es-

pecially if acute lung injury was present [7]. Posttraumatic stress disorder has also been observed in these patients [8]. Long-term follow-up of patients in this study and others similar to it is needed to determine the residual impact, if any, of this sedation strategy.

Ostermann Me, Keenan SP, Seiferling RA, Sibbald WJ (2000) Sedation in the intensive care unit: a systematic overview. JAMA 283:1451–1459

In this paper the authors performed a systematic review to determine what medications are associated with best sedation, shortest time to extubation, and shortest ICU stay. Their strategy to locate studies included searching computerized databases, hand-searching key journals, writing to experts in the field, consulting personal files, and examining reference lists of retrieved articles. Selected articles fulfilled the following criteria: (a) enrollment of adult patients requiring mechanical ventilation and short or long-term sedation, (b) comparison of at least two sedative drugs, (c) outcomes included were quality of sedation, time to extubation, or ICU length of stay, and (d) randomized study design. Two of the investigators independently appraised the included articles using standard methodological criteria. They identified 32 randomized controlled trials that met the inclusion criteria and separated them into groups according to the required duration of sedation, the patient population (cardiac surgery vs. other ICU patients), and agents being compared. Because there was significant heterogeneity among trials, their results were not combined statistically, but descriptive results data from each are displayed.

The most striking result of this overview is the demonstration of the paucity of data available on the choice of sedatives in the ICU. Most studies compared midazolam with propofol. Of the 32 studies only 14 followed patients for longer than 24 h. With the exception of trials evaluating patients following cardiac surgery no data are available about the effect of sedative choice on the duration of mechanical ventilation. Similarly, data examining length of stay in the ICU are extremely limited and do not allow any conclusions to be reached.

This paper has reasonable internal validity. The authors performed an exhaustive search for relevant articles, independently appraised those critically that were included, and did not attempt to group heterogeneous studies. Although the lack of data would have precluded any meaningful meta-analytic statistics being generated, we feel that the authors were destined to find very heterogeneous results by asking too broad a clinical question. While they appropriately specified the patient population, interventions, and outcomes of interest, their respective choices likely predetermined finding heterogeneous results. Clearly the study of sedation in patients following cardiac surgery is very different from that in patients with acute lung injury, although both groups do require mechanical ventilation. One additional question is whether their inclusion criteria were selected a priori or were determined after the trials had been retrieved.

Discussion

The data from both the Brook et al. [9] and Kress et al. [10] studies seem to indicate that the manner in which sedatives are used in the ICU is important when examining important clinical and cost-related outcomes such as duration of mechanical ventilation and length of hospital or ICU stay. The methodological issues raised above for each of these studies may diminish the demonstrated effect size slightly, but likely do not influence this conclusion. The fact that the two studies demonstrated comparable results is reassuring in this regard. The process of implementing sedation in critically ill patients may be equally or more important than the choice of which sedative drug to use. The data from the Ostermann et al. [11] overview eloquently demonstrate that at the current time we are unable to answer this question because so few data are available comparing different sedatives and examining clinical outcomes in a rigorous fashion.

Based on these data we believe that consideration should be given to composing and utilizing sedation protocols in many ICUs. These are probably best developed in a multidisciplinary manner, with input from physicians, nurses, pharmacists, and respiratory therapists. At the very least, however, quality assurance studies should be performed in the individual ICUs to ensure that their results are consistent with the published experience.

Many important questions regarding sedation in the ICU remain unanswered. First, the reproducibility of the protocols described above and their results needs to be demonstrated. Whether daily interruptions, daily decreases in sedative infusions or a combination of these are the key to the results in the Kress et al. study also should be tested. Given the high costs of both ICU stay and sedative drugs, a full economic analysis with consideration of the human resource impacts would be welcome. Finally, the long-term effects of these strategies need to be evaluated, and the impact of a potentially "lighter" degree of sedation on patients' long-term health-related quality of life should be determined. Future studies comparing individual sedatives and examining clinical outcomes are also needed.

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