A prospective evaluation of empiric versus protocol-based sedation and analgesia

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The introduction of a protocol determining the administration of sedatives and analgesics to patients in a medical-surgical-neurologic intensive care unit (ICU). The protocol for patients under short-term sedation, (less than 48 hours), promoted propofol by continuous infusion, with midazolam as an alternative if hypertriglyceridemia or cardiovascular instability was present. For patients under long-term sedation, Lorazepam was preferred, with bolus doses of midazolam for acute anxiety or restlessness. If patients required frequent neurological assessments, propofol infusion was continued. For analgesia, morphine was preferred, with fentanyl given as an alternative for patients with haemodynamic instability, morphine allergy or renal insufficiency. Codeine was recommended for patients requiring frequent neurological assessments. For delirium, haloperidol was recommended. The results of the protocol were compared with previous practice, when staff would have acted in a more independent and less uniform way.

Type of intervention
Treatment guidelines.

Economic study type
Cost-effectiveness analysis.

Study population
Patients in the medical-surgical-neurologic ICU of a hospital, who required continuous sedation for at least 6 hours.

Setting
Secondary care. The economic study was carried out in Canada.

Dates to which data relate
No dates were given for effectiveness evidence, or resources used. The price year was not reported. The evidence was collected over a 9 month period before April 1999.

Source of effectiveness data
The estimates of effectiveness were derived from a single study.

Link between effectiveness and cost data
Prospective costing was undertaken alongside the effectiveness study and on the same patient sample.

Study sample
Power calculations were carried out and it was found that, for a power of 0.8 and a significance level of 0.05, a total sample of 140 was required, based on costs. The total number of patients included in the study was 158: 72 during...
empiric therapy and 86 during protocol based therapy. Patient consent was not requested and all patients requiring continuous sedation for at least 6 hours were included.

Study design
This was a non-randomised trial with historical controls that took place in one centre. Patients were only studied while they were in the ICU, and were not studied after they left it.

Analysis of effectiveness
The analysis was based on intention to treat. The primary health outcomes used were a modified Ramsay Sedation Score, modified visual analog pain measurement, duration of mechanical ventilation, length of ICU stay, time between sedation discontinuation and tracheal extubation and time between sedation discontinuation and ICU discharge. The patients in the two groups were assessed for comparability and were shown to be similar with respect to demographic data, ICU admission criteria, APACHE II scores, duration of ventilation and length of ICU stay. Among patients receiving long-term sedation, the protocol group had fewer admissions involving neurologic etiologies than the empiric group. This characteristic did not seem to affect the health outcomes that were measured.

Effectiveness results
11% of patients in the protocol group experienced anxiety, agitation, restlessness or confusion (Ramsay score 1), compared to 22.4% in the empiric group, (p<0.05). The protocol group was more frequently maintained at a modified Ramsay sedation score of 4, (29.6%), in comparison to the empiric group, (17.2%), (p<0.01). The protocol group experienced less pain (5.9% versus 9.6%, p<0.05), measured as the percentage of measurements with a score \( \geq 1 \).

Among the group of patients receiving short-term sedation, (less than 48 hours), 37.6% were maintained at a modified Ramsay score of 4 in the protocol group, as compared to 19.3%, (p<0.1) in the empiric group.

Among the patients receiving long-term sedation, 25.7% were maintained at a modified Ramsay score of 4 in the protocol group, as compared to 15.7%, (p<0.05), in the empiric group. The protocol group experienced less pain, 5.3% versus 10.3%, (p<0.05).

In terms of the duration of mechanical ventilation and length of ICU stay the differences between the two groups were not statistically significant. However, the results showed that patients under long-term sedation in the protocol group spent a longer time between sedation stopping and extubation: 77.2 hours (SE, 97.9) compared to 54.4 hours (SE, 64.3) in the empiric group.

Clinical conclusions
Patients receiving long-term sedation experienced less anxiety and pain when their medication was determined by the protocol.

Measure of benefits used in the economic analysis
The authors derived no single measure of benefit, and the study used a cost-consequences approach.

Direct costs
The pharmaceutical costs of analgesia and sedation were included in the analysis. As the study took place over a short period (less than 1 year) discounting was not relevant. Quantities and costs were not analysed separately. The estimation of costs was based on actual data from the hospital in which the study was carried out. The date of the cost data was not given. No price year was given and no price reflation was carried out. However, as the study took place within one year it is possible that no large relative price changes took place. No differences between marginal and average costs were calculated. The cost of preparing lorazepam infusions and of wasted lorazepam from precipitation was not included as it was assumed to be insignificant. It was assumed that the costs of implementing the protocol were not significant.
Sedation and pain assessments were recorded more frequently under the protocol, and this cost of administration was not included, as it had not been foreseen. Only pharmaceutical costs were measured: non-pharmaceutical costs in the ICU were not measured.

**Statistical analysis of costs**
Costs were reported as mean +/- SD. Parametric data were analysed using unpaired or two-tailed Student’s t test and non-parametric data were compared using Mann-Whitney U test.

**Indirect Costs**
No indirect costs were included.

**Currency**
Canadian dollars (Can$).

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
Not applicable.

**Cost results**
The only costs recorded were total pharmaceutical costs. The pharmaceutical costs of sedation and analgesia changed from Can$615.69 (SE 744.29) for the empiric group to Can$627.80 (SE 1051.73) for the protocol group; this figure for all patients masks an important difference between the two types of patients. Short-term patients’ costs went from Can$164.09 (SE 156.70) to Can$173.35 (SE 155.91), whereas long-term patients’ costs went from Can$976.97 (SE 829.338) to Can$43.78 (SE 1,231.46). The authors focussed on the hourly cost of sedation under the two regimes, showing that it changed from Can$7.69 (SE 5.29) to Can$5.68 (SE 4.27), (p<0.01). The result for short-term patients was a change from Can$7.82, (SE 6.29) to $7.04 (SE 5.42), and for long-term patients a change from $7.59 (SE 4.40) to $4.98 (SE 3.40). The costs of extra monitoring under the protocol and the costs of learning and adopting the protocol were not recorded. The average cost of a patient day in the ICU in different conditions was not recorded.

**Synthesis of costs and benefits**
Not applicable.

**Authors' conclusions**
The pharmaceutical protocol introduced to the medical-surgical-neurological ICU of the Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada reduced drug costs and enhanced the quality of sedation and analgesia for patients requiring long-term sedation. The latter group of patients spent a longer time between cessation of sedation and extubation, but no longer between sedation cessation and discharge from the ICU.

**CRD COMMENTARY - Selection of comparators**
The authors were comparing the introduction of a protocol for administering sedatives and analgesics with what had been current practise in the ICU of their hospital (the comparator). The authors point out that the time during which data were collected for what had been current practise was also the time when thought was being given to introducing a new protocol. It is therefore possible that practise during those four months under study was not identical to practise in the preceding the study period.
Validity of estimate of measure of effectiveness
There was no sample selection of patients under study as all patients during the time period under study were included. Patients in the two time periods were shown to be comparable in terms of demographic status and medical condition except that, under the protocol, there were more patients requiring long-term sedation suffering from neurological etiologies. This difference was found not to have any effect on the variables under study. Patients were evaluated more frequently when the protocol was being applied, therefore this may have affected outcomes independently of the change in policy regarding pharmaceuticals. The choice of measures to evaluate the effectiveness of sedation and analgesia was argued for by the authors. It would have been helpful to have assessed patient well-being at time of discharge from ICU, and at a follow-up period after leaving the ICU.

Validity of estimate of measure of benefit
The authors used no single benefit measure, therefore the study used a cost-consequences approach.

Validity of estimate of costs
Not all relevant categories of cost were included in the analysis. The authors focussed on the hourly pharmaceutical cost of sedation, whereas they should have concentrated on the total pharmaceutical cost and the total non-pharmaceutical cost. They excluded the time taken to learn and apply the protocol which they considered was insignificant. The extra monitoring time under the protocol, which they had not anticipated, was not costed. They did not cost the time spent in the ICU under sedation, between sedation and extubation and between extubation and discharge. These costs could be important evidence if further study shows that the protocol does increase the amount of time spent under sedation in the ICU for patients requiring long-term sedation. Although the differences in time reported in this study were not statistically significant, a study with a larger sample size might find significant differences. Also when the authors gave details of pharmaceutical use under the two regimes they only gave total costs with no breakdown of quantities and prices. It would have been interesting to have seen how the quantity of medication varied under the two regimes, and the extent to which changes in costs were due to differences in pharmaceutical prices. As pharmaceutical prices can change over time, it is important to know their role in these results. The authors did not include the cost of wasted lorazepam from precipitation or the cost of nonpolyvinylchloride containers but argue that it was minimal in comparison with the pharmacological costs.

Other issues
The authors gave a comprehensive account of the existing literature in this area, and gave a good justification for the need to carry out this study. They were very aware of some of the limitations of their study: they acknowledge the need for a randomised controlled trial of the protocol regime and they are aware that the results are institution specific so that there is a need for studies carried out in a range of settings. They do acknowledge that non-pharmaceutical patient costs in the ICU could be important.

Implications of the study
There is clear evidence that a protocol based regime of sedation and analgesia changed the medication received by patients in the ICU. The patients under long-term sedation were administered more lorazepam and less propofol. The evidence on length of time under sedation in the ICU for the latter group of patients is unclear, as there was obviously a large variation. It would be useful to have a study with a larger sample to establish whether or not the protocol did increase the length of stay. The pharmaceutical costs of the long-term sedated went down under the protocol. The authors recommend a randomised controlled trial, but all the costs should be calculated in such a trial. Also a more comprehensive assessment of patient's health at discharge and after a follow-up period would make any results more valuable. The authors point out that their results are specific to their institution and it would be useful if a study could take place at more than one centre, so that any results could have more general validity.

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