Pharmacoeconomic impact of rational use guidelines on the provision of analgesia, sedation, and neuromuscular blockade in critical care
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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
Guidelines for the provision of continuous analgesia, sedation, and neuromuscular blockade for critically ill patients requiring ventilator management. In this research the guidelines used a five-step process that included evaluation, analgesia, sedation, neuromuscular junction blockade, and dosage adjustment. A distinct end point for each class of agents was preserved. An academic detailing process was used to educate practitioners about the use of guidelines. Daily interventions were performed, and the prescribers were made aware, by direct and written communication, when their regimens varied from the suggested guidelines. The cost implications of such deviations were also brought to the attention of the prescribers.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients admitted to medical and surgical intensive care units (ICUs) who required mechanical ventilation and continuous analgesics, sedatives, and/or neuromuscular junction blockers (NMJBs).

Setting
Hospital. The economic analysis was carried out in the USA.

Dates to which data relate
Effectiveness and resource use data for the baseline patients (before the implementation of guidelines) were collected from 3 March 1995 to 15 September 1995. Data for the follow-up group were collected from 19 June 1996 to 22 September 1996. The price year appears to have been 1995-96.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing was prospectively performed on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were not used to determine the sample size. The study sample consisted of 72 patients in the
baseline group with a mean age of 57.17 (range: 12 - 91) years and 84 patients in the follow-up group with a mean age of 56.7 (range: 15 - 92) years. The subgroup of patients with tracheostomy and prolonged ventilation consisted of 18 patients in the baseline group (mean age 52.6 years) and 14 patients in the follow-up group (mean age 51.42 years).

**Study design**
This was a non-randomised study with historical controls, carried out in a single centre. The duration of the follow-up appears to have been until discharge. There appears to have been no loss to follow-up. Prospective tracking of eligible baseline patients was followed by the development and introduction of guidelines and an academic detailing process to promote the use of these guidelines. Several months after the introduction of guidelines, the second group of eligible follow-up patients was tracked.

**Analysis of effectiveness**
The principle used in the analysis of effectiveness (intention to treat or treatment completers) was not explicitly specified. The clinical outcomes were adverse drug reactions, functional status, ventilator time in hours, length of stay, use of NMJBs, and mortality rate. Functional status was recorded so that the potential long-term impact of the guidelines on the patient's discharge status (and in particular, prolonged weakness from NMJBs) could be considered. An assessment of daily living variables was used to classify discharged patients into one of the following functional status categories: alive/full function, alive/rehabilitation, alive/disability, or dead. Both groups were similar with regard to demographics.

There was a statistically significant increase in severity of illness in the follow-up group. To verify that the study data were not skewed by a population of patients with a traditionally extended length of stay, the authors studied a subgroup of patients with tracheostomy and prolonged ventilation (diagnosis-related group (DRG) 483) to examine the impact on the data from this critically ill subgroup.

**Effectiveness results**
The mean ventilator time was 317 hours in the baseline group and 167 hours in the follow-up group. The mean length of stay was 34.3 days in the baseline group with 19.1 days in the intensive care unit. In the follow-up group the mean length of stay was 23.3 days with 9.9 days in the intensive care unit. The mortality rate was 16.7% in the baseline group and 17.6% in the follow-up group, (p=0.89). The use of NMJBs was reduced from 30% (22/72) in the baseline group to 5% (4/84) in the follow-up group, (p<0.001). There were no documented cases of prolonged weakness in the follow-up group. There was a very high mortality rate in patients who received NMJBs in both the baseline and follow-up groups: 8 out of 22 baseline patients (36.4%), and 2 out of 4 follow-up patients (50%), died. Similar outcomes were found when DRG 483 was compared with the entire cohort. However, no significant change in length of stay or ICU length of stay was noted in DRG 483. The functional status data appeared to indicate an improvement in outcomes in the follow-up group. There was a reduction in the number of patients who required rehabilitation in the follow-up group when compared with the baseline group.

**Clinical conclusions**
The study demonstrates that the use of a set of rational guidelines for analgesia, sedation, and NMJBs is safe and effective. Furthermore, the authors observed a dramatic decrease in the frequency of NMJB use, which was an unexpected, but not surprising, finding in a population given optimal analgesic and sedative doses before the introduction of NMJBs. There were no documented cases of prolonged weakness in the follow-up group, despite the preferential use of pancuronium bromide in these patients. Subgroup analysis verified the results achieved in the main analysis.

**Measure of benefits used in the economic analysis**
No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were reported, as shown in the effectiveness results above.
Direct costs
Costs were not discounted due to the short time frame of the cost analysis. Some quantities were reported separately from the costs. Cost items were not reported separately. Cost analysis covered the costs of drugs classified as narcotics, benzodiazepines, propofol (less than 24 hours), propofol (over 24 hours), and neuromuscular junction blockers. The perspective adopted in the cost analysis appears to have been that of the hospital. The drug costs were based on daily mean and maximum acquisition costs. The price year appears to have been 1995-96.

Indirect Costs
Indirect costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analysis was conducted.

Estimated benefits used in the economic analysis
Not applicable. The reader is referred to the effectiveness results recorded above.

Cost results
The mean (maximum) drug costs per day are shown below.

Narcotics: baseline group, $28.28 ($424); follow-up group $6.94 ($91.48).

Benzodiazepines: baseline group, $146.72 ($1,080); follow-up group and $50.19 ($222.77).

Propofol (less than 24 hours): baseline group, $31.45 ($143.03); follow-up group, $21.27 ($146.29).

Propofol (over 24 hours): baseline group, $355.82 ($1,010.88); follow-up group, $123.06 ($460.50).

Neuromuscular junction blockers: baseline group, $441.17 ($1,721); follow-up group, $45.88 ($182.23).

Synthesis of costs and benefits
Costs and benefits were not combined.

Authors' conclusions
Rational use guidelines resulted in safe, cost-effective improvements in the provision of continuous analgesia, sedation, and neuromuscular blockade for critically ill patients requiring ventilator management when compared with similar factors in baseline prescribing strategies.

CRD COMMENTARY - Selection of comparators
The strategy of not implementing rational use guidelines (baseline prescribing strategies) was explicitly regarded as the comparator. This allowed the active value of the intervention to be evaluated.

Validity of estimate of measure of effectiveness
The effectiveness results are likely to be internally valid, given the prospective nature of the study design and minimal
provider awareness. Despite the randomised controlled trial being the ideal design, it was deemed to be limited by the effect of the intervention on data collection, because it is virtually impossible to blind such a study. The authors believed that, because of the inherent limitations associated with the nature of critical care, which rendered a blinded, controlled, clinical trial virtually impossible, this study, to date, represented the best available information on the subject. The adequacy of the study sample size to address the main study questions is open to doubt in view of the absence of power calculations. While the study groups were similar in terms of demographics, they were significantly different with respect to severity of illness. The study sample does, however, appear to have been representative of the study population.

Validity of estimate of measure of benefit

The authors did not derive a measure of health benefit. The study was therefore a cost-consequences analysis.

Validity of estimate of costs

The validity of the cost results was enhanced by the following features of the cost analysis: some quantities were reported separately from the costs; the price year and the perspective adopted in the cost analysis were specified; the cost calculations were based on acquisition costs; and statistical analysis was performed on some resource use data. However, the validity may have been limited by the following factors: the cost analysis does not appear to have been comprehensive as some components of total costs, such as the costs of the intervention programme, were not included in the analysis; no statistical analysis appears to have been performed on cost data; the effects of the intervention programme on indirect costs (productivity loss) were not addressed; and the cost results may not be generalisable outside the study setting.

Other issues

Given the limitations of the study design, some degree of caution may need to be exercised in interpreting the results. The issue of generalisability to other settings or countries was not addressed, but appropriate comparisons were made with other studies. The degree to which the study sample was representative of the study population was not addressed. Further limitations of the study were noted by the authors.

Although the study was performed on a daily and prospective basis, the interactions and education with the prescribers did not occur immediately. This forced frequent changes in orders that had already been initiated;

Conclusions regarding adverse drug reactions were limited by the number of concomitant diseases that produce symptoms similar to those caused by adverse drug events.

Adverse effect assessment was based on clinical and functional assessment rather than a comprehensive work-up to determine any causal relationships.

Finally, the clinical research nurse collecting data was not blinded.

Implications of the study

One possible line of future research would be to examine the impact on cost and outcome of compliance versus non-compliance with guidelines; the major advantage of such an approach would be that it could provide routine information on cost and outcomes in conjunction with provider feedback. Further pharmacoeconomic research is needed to determine the impact of guidelines on other pharmacotherapeutic agents commonly used in the critical care settings.

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