The effect of timing of ondansetron administration on its efficacy, cost-effectiveness, and cost-benefit as a prophylactic antiemetic in the ambulatory setting


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 health technology studied was ondansetron in various doses and stages of administration in the prevention and treatment of postoperative nausea and vomiting (PONV).

Type of intervention
Primary prevention; Treatment.

Economic study type
Cost-effectiveness analysis; Cost-benefit analysis.

Study population
The study population comprised women scheduled for outpatient laparoscopic procedures. The exclusion criteria were as follows: patients who had taken an antiemetic or psychoactive medication within 24 hours before surgery; who were more than 50% above their ideal body weight; who were pregnant; or who were experiencing vomiting or retching within 24 hours before surgery.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The dates of effectiveness, resource use and prices were not reported.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Prospective costing was carried out on the same patient sample as that used in the effectiveness analysis.

Study sample
The power calculations performed showed that a sample size of 40 patients in the placebo and treatment groups was sufficient to show a decrease in the incidence of PONV from 65% in the placebo group to 30% in the treatment group with alpha=0.05 and beta=0.2. 164 patients scheduled for outpatient laparoscopic procedures were enrolled in the study and were randomised to the four study groups. 8 patients were excluded from the analysis (5 patients had open surgical procedures after laparoscopy, and there were protocol violations in the treatment of 3 patients). There were 39 subjects in the placebo group (Group A), 38 in the group receiving ondansetron 2 mg at the start of and 2 mg after surgery.
(Group B), 39 in the group receiving ondansetron 4 mg before induction (Group C), and 40 in the group receiving ondansetron 4 mg after surgery (Group D). The baseline characteristics, including demographic and clinical characteristics, were presented.

**Study design**

A double blind, placebo-controlled, randomised, controlled trial was performed. Subjects were randomised to one of the four treatments using a computer-generated random number table. Patients were followed during the operation and were contacted 24 hours and 7 days after the operation. Investigators, blinded to patients' treatment group, recorded the intra-operative, recovery variables and post surgery outcomes. 6 patients could not be contacted after surgery (2 in group A, 3 in group C, and 1 in group D) and were excluded from the post discharge and 24 hour analyses.

**Analysis of effectiveness**

The analysis was based on treatment completers only. The groups were shown to be comparable (p>0.05) at baseline with respect to age, weight, height, racial background, number of days since the start of their last menstrual period, duration of anaesthesia and surgery, and history of PONV and motion sickness. The primary health outcome was a complete response to prophylactic antiemetic medication defined as no vomiting, no rescue antiemetic medication, and no-withdrawal from study during the 24-hour postoperative study period. The effectiveness measure was defined as the number of patients with both a complete response and no side-effects from antiemetic drugs.

Additional outcome variables included time (minutes) to eye opening, tracheal extubation, response to verbal commands, orientation, time to first oral intake, ambulation, being judged fit for discharge, actual discharge, and time from the end of anaesthesia to the time when 25% of patients in each group failed prophylactic antiemetic therapy. Patients completed a visual analogue scale (VAS) for sedation, fatigue, comfort, pain, and nausea using a 100-mm scale (0 = none to 100 = maximum). The VAS was completed at baseline, 2 hours after the procedure and immediately before discharge from hospital. The quality of sleep (normal, intermittent, restless), time taken off work by a caretaker (days), time taken to return to work (days); time taken to tolerate regular fluids (day of surgery, one day after, more than two days after) and normal food (day of surgery, one day after, two days after, more than three days after), as well the patient's satisfaction (highly satisfied, satisfied, no opinion, dissatisfied) with the control of PONV after the operation and willingness to pay to prevent PONV, were also assessed.

**Effectiveness results**

Due to the large number of separate results, only those with +/- significant difference will be given here.

The times of eye opening, tracheal extubation, response to verbal commands, and orientation, as well as the VAS scores for sedation, fatigue, comfort, and pain at baseline or 2 hours after surgery were not significantly different among the four groups.

Ondansetron 4 mg after surgery reduced the time to first oral intake (106 +/-38 versus 132 +/-49), ambulation (159 +/-46 versus 204 +/-64), being judged fit for discharge (168 +/-48 versus 213 +/-61), and the time to discharge (198 +/-61 versus 243 +/-71) compared with the placebo.

Ondansetron 4 mg before anaesthesia reduced the time to discharge compared with the placebo (207 +/-64).

The number of patients with complete responses was significantly greater in the groups receiving 4 mg ondansetron before induction or after surgery compared with the placebo and split dose groups (16 in group A, 16 in group B, 25 in Group C and 25 in group D).

The time (in minutes) from the end of anaesthesia to the time when 25% of patients in each group failed prophylactic antiemetic therapy was significantly increased in Group D compared with the other groups (178 for group A, 265 for group B, 421 for group C, and more than 1,440 for group D).

4 mg ondansetron after surgery resulted in significantly lower verbal nausea assessment score at 24 hours compared to all other groups (1.0 +/-2.3 versus 4.5 +/-4.2 for group A, 3.0 +/-4.1 for group B, and 3.1 +/-4.1 for group C).
There were stated to have been no significant differences in the incidence of nonemetic postoperative side-effects among the four treatment groups, although no data were given.

After discharge the quality of sleep, time taken off work by a caretaker, and time to return to work were not significantly different among the four groups.

4 mg ondansetron administered after surgery resulted in significantly decreased times taken to tolerate regular fluids compared with placebo and split dose (30 patients in group D resumed oral fluids on the day of surgery versus 21 in each of groups A and B) and to tolerating normal food, compared with all other groups (21 in group D resumed normal food on day of surgery versus 12 in each of groups A, B and C).

Clinical conclusions
Ondansetron 4 mg administered at the end of surgery and pre-induction is statistically significantly more effective in preventing PONV in the post anaesthesia care unit (PACU). Ondansetron 4 mg post surgery resulted in statistically significant improvement in other outcomes, including time to discharge, patients nausea score, and time to resume fluids and food in the post discharge period.

Modelling
A decision tree model published elsewhere was employed to assess the cost-effectiveness. Please see Other Publications of Related Interest at the end of this abstract.

Measure of benefits used in the economic analysis
The measures of benefits used in the economic analysis were the number of patients with both a complete response and no side-effects from antiemetic drugs (for the cost-effectiveness analysis), and the patients' willingness to pay to prevent PONV if they underwent a similar operation in the future (for the cost-benefit analysis) ($0, $50, $100, $250 or other).

Direct costs
The direct costs considered in the analysis were from the perspective of the health care provider. Resource use and cost data were based on the setting of the study. These included costs for "emesis clean-up", rescue antiemetic therapy, management of side-effects of prophylactic and rescue antiemetic therapy, and the acquisition cost and materials used for administering prophylactic drugs. The costs for acquisition of drugs, and the labour costs according to the place of emesis or managing of side-effects were considered. Resource quantities were given only in terms of procedure time, but without corresponding unit costs.

Statistical analysis of costs
The costs were treated stochastically, and were analysed with a one-way analysis of variance.

Indirect Costs
No indirect costs were analysed.

Currency
US dollars ($).

Sensitivity analysis
The parameter varied in the sensitivity analyses was the effect of excluding nursing-labour costs on the cost-effectiveness ratios.
Estimated benefits used in the economic analysis
The incremental effectiveness was not explicitly reported. The numbers of patients with complete responses in different groups were reported (see effectiveness results above), but those for the side-effects from antiemetics were not given. Patients were willing to pay a mean of $117+/-$82 to prevent PONV if they underwent a similar operation in the future.

Cost results
The costs were not presented by treatment group. Only the overall weighted costs per patient for the management of PONV (including administering prophylactic and rescue antiemetics, emesis clean-up costs, and costs of managing side effects) of $21+/-$7 were given.

Synthesis of costs and benefits
The average cost-effectiveness ratios were as follows: Group A $53 (95% CI: $26 - $79), Group B $64 (95% CI: $39 - $89), Group C $46 (95% CI: $31 - $61) and Group D $36 (95% CI: $26 - $45).

If the nursing costs were excluded the cost-effectiveness ratios would be $21 (95% CI: $10 - $33) for Group A, $45 (95% CI: $28 - $63) for Group B, $35 (95% CI: $24 - $46) for Group C, and $28 (95% CI: $20 - $36) for Group D.

The benefits-to-cost ratio was stated to have been 5:1.

Authors' conclusions
The authors concluded that ondansetron 4 mg administered before the end of surgery was more effective in preventing PONV, facilitating both early and late recovery, and improving patient satisfaction after outpatient laparoscopy and that "the routine use of prophylactic ondansetron administered at the end of surgery was more cost-effective than a strategy of reserving it for persistent emesis after failure of a metoclopramide rescue in the PACU."

CRD COMMENTARY - Selection of comparators
The authors justified the choice of ondansetron and interventions with different timings as a treatment without the side-effects of other antiemetics. Placebo was also used as a comparator, but without justification. The user of the database should consider the usual practice in their own setting to assess the transferability of this study's results.

Validity of estimate of measure of effectiveness
The analysis was based on a double-blind randomised controlled trial, which was appropriate for the study question, although the method of randomisation was not given. The degree to which the study sample was representative of the study population may be assessed by reference to the baseline characteristics presented, and the groups were comparable at baseline. The effectiveness was analysed on the basis of treatment completers only, although only six patients were lost to follow-up. The study was powered to detect differences in incidence of PONV, but it is not clear that this is the same as "complete response", and the lack of statistically significant difference in other measures may have been due to lack of power. The problem with effectiveness measurement is compounded by the lack of reported results for the side-effects of the anti-emetics.

Validity of estimate of measure of benefit
For the cost-effectiveness analysis, the estimation of benefits was obtained directly from the effectiveness analysis. Therefore, please see the above commentary. As the authors acknowledge, analysis of a willingness to pay could have missed important determinants of the valuation, and may have been biased by the scale used.

Validity of estimate of costs
All categories of costs relevant to the perspective adopted appear to have been included in the analysis. However, costs
and quantities were not reported separately and neither were total costs per group. This is a serious flaw in the presentation of the results, especially since a no incremental analysis was performed. A decision on adoption of the technology should be made with information on the incremental benefit (from next best to new technology) or effectiveness and resource use or monetary cost. In this study only average cost-effectiveness ratios, which indicate the change from a state of no current technology, are presented. The authors used the decision rule to implement that with the lowest ratio. However, a lower ratio can be due to a variety of incremental changes with variable value, for example with lower benefit and lower cost, or higher benefit and higher cost. It can only be presumed that group D is the more costly alternative, given that it had the greatest benefit and the lowest average cost-effectiveness. Unfortunately, without knowing how much more costly, assessment of willingness to pay would not be possible. The dates of resource use data and prices were also not reported.

Other issues
The authors compared their results with those from other studies in terms of effectiveness and timing of the intervention but not in terms of cost-effectiveness and benefit. The issue of generalisability to other settings was not addressed. The authors did not present sufficient results in order to support their conclusions, particularly in terms of costs, but also for effectiveness.

Implications of the study
The authors concluded that ondansetron 4 mg should be administered at the end of operation and not before induction as recommended by the manufacturer. However, this conclusion should be viewed in the light of the methodological flaws outlined above.

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Other publications of related interest


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