The effect of intravenous opioid patient-controlled analgesia with and without background infusion on respiratory depression: a meta-analysis

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CRD summary
The review concluded that limited and variable evidence showed that addition of a background infusion to demand dose for intravenous patient-controlled analgesia (IV-PCA) regimen was associated with a higher rate of respiratory depression than demand IV-PCA alone in adults but not in children; this result was subject to uncertainty. These cautious conclusions are likely to be reliable.

Authors' objectives
To assess whether the addition of a background infusion to an intravenous patient-controlled analgesia (IV-PCA) regimen was associated with an increased risk of respiratory depression.

Searching
PubMed was searched from inception to November 2008 without language restrictions. Search terms were reported. Reference lists of retrieved studies were screened.

Study selection
Randomised controlled trials (RCTs) that compared demand patient-controlled analgesia with a background infusion versus demand patient-controlled analgesia without a background infusion were eligible for inclusion. Delivery of opioid medication had to be administered intravenously. The primary outcome was respiratory depression (the authors adopted multiple definitions from the original trials). Secondary outcomes were pruritis, sedation, pain, postoperative nausea and vomiting and opioid consumption.

All the trials assessed the addition of a background infusion of morphine with varying doses to an intravenous patient-controlled analgesia regimen in their intervention arms. The control arms of these trials assessed the demand dose regimen consisting of morphine, oxymorphone or pethidine, with varying doses every five to 20 minutes. Definitions of respiratory distress varied between studies; most studies used respiratory rate of less than eight to 12 breaths per minute to define respiratory distress. Most of the included trials recruited adults only; two trials recruited children and one trial recruited mixed adults and children.

Two reviewers independently assessed studies for inclusion. Any disagreements were resolved by discussion.

Assessment of study quality
The authors did not state that they assessed study quality.

Data extraction
Data were extracted on event rates for each treatment group to enable calculation of odds ratios (OR) with 95% confidence intervals (CI). Where necessary, data were estimated and extrapolated from figures and tables.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
The random-effects model was used to calculate the pooled odds ratios with 95% CI. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$ statistics. Subgroup analyses were conducted for adults and children.

Results of the review
Fourteen RCTs were included (796 patients): 11 trials of adults, two trials of children and one trial of adults and children.

Compared with IV-PCA with demand dose only, addition of a background infusion to the demand dose for IV-PCA
with opioids was significantly associated with an increased rate of respiratory depression (OR 4.68, 95% CI 1.20 to 18.21; 14 RCTs). Moderate heterogeneity was found for this outcome ($I^2 = 49.5\%$). There were no significant differences between treatment groups in terms of the rates of pruritis (seven RCTs) and sedation (four RCTs) with no significant heterogeneity observed in the two outcomes.

Subgroup analyses showed similar results on the rate of respiratory depression in adults (OR 10.18, 95% CI 2.97 to 34.89; 11 RCTs, 674 participants) but there was no significant difference between treatment groups for studies in children (OR 0.68, 95% CI 0.16 to 2.96; three RCTs, 122 participants). No significant heterogeneity was observed in these outcomes.

Data on other outcomes (pain, postoperative nausea and vomiting and opioid consumption) were too heterogeneous to permit pooling. However, eight out of 10 trials studies reported a significant increase in the use of morphine in the groups that received a background infusion.

**Authors’ conclusions**
Addition of a background infusion to the demand dose for IV-PCA was associated with higher rates of respiratory depression than demand IV-PCA alone in adults but not in children. These findings should be interpreted with caution due to the small sample size and wide range of definitions for respiratory depression.

**CRD commentary**
The review question was clear and supported by appropriate inclusion criteria. Only one relevant database was searched so relevant studies may have been missed. No specific attempts were made to locate unpublished studies and this introduced potential for publication bias. Appropriate steps were made to minimise bias and errors during study selection; it was unclear whether similar steps were performed for data extraction. No formal quality assessment was performed but the authors discussed some aspects of study quality (such as small sample sizes in most trials). Only limited details of the included studies were presented. Heterogeneity was assessed and appropriate methods were used to pool results.

The authors’ conclusions acknowledge the limitations of data and reflect the evidence presented. These cautious conclusions are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that for adult patients, addition of a background infusion to IV-PCA may be more suitable in patients who are opioid-tolerant or in opioid-naive patients with high-opioid requirements.

**Research:** The authors stated that the findings from this review should be used to generate hypotheses for future research.

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