Efficacy of fentanyl iontophoretic transdermal system in postoperative pain: a meta-analysis

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CRD summary
The authors concluded that the fentanyl iontophoretic transdermal system appeared safe and was more effective than placebo for acute postoperative analgesia; it was unclear whether it is as effective as morphine patient-controlled analgesia. Potential publication bias and poor reporting of study characteristics, study quality and review methods mean that the authors’ conclusions may require cautious interpretation.

Authors' objectives
To evaluate the efficacy and safety of the fentanyl iontophoretic transdermal system (ITS) for acute postoperative pain.

Searching
MEDLINE (from 1966), Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and CINAHL were searched to June 2008 with no language restrictions. Search terms were reported. Reference lists of relevant articles were checked. The search was limited to studies published in full.

Study selection
Randomised controlled trials (RCTs) that compared fentanyl ITS with placebo or morphine patient-controlled analgesia (PCA) for acute postoperative pain were eligible for inclusion.

Participants in the review had undergone major abdominal, orthopaedic, thoracic or pelvic surgery. Outcome measures in primary studies included dropout rates (overall and due to inadequate analgesia), pain relief (using the Patient Global Assessment scale), pain intensity (using a visual analogue scale or Pain Numeric Rating Scale) and adverse effects (such as nausea, pruritus, headache, respiratory depression). All included studies were industry sponsored.

One author screened study abstracts and selected potentially relevant publications. These were checked for eligibility by two reviewers independently.

Assessment of study quality
Study validity was assessed using the Jadad Scale and Oxford Pain Validity Scale (OPVS). The Jadad scale assessed adequacy of reported randomisation, double blinding and withdrawals or dropouts to a maximum of five points. OPVS assessed quality of blinding, sample size, outcomes measurement and data analysis to a maximum of 16 points.

Two reviewers independently conducted validity assessment. A third reviewer resolved disagreements.

Data extraction
For each study, odds ratios (ORs) were extracted or calculated for dichotomous outcomes and mean differences for continuous outcomes, with 95% confidence intervals (CIs). Means and standard deviations were extracted from graphs and standard deviations were calculated from standard errors, as required. Pain Numeric Rating Scale was converted from a one to 10 scale to a one to 100 scale.

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

Methods of synthesis
Studies were combined to calculate pooled odds ratios, weighted mean differences (WMDs) and 95% CIs. A fixed-effect model was used unless statistical tests for heterogeneity were positive, in which case it was planned to use a random-effects model.

Results of the review
Six RCTs were included in the review (n=3,270). Jadad scores were 2 (one RCT) or 3 (five RCTs) out of a possible 5 points. OPVS scores were 9, 10 or 12 points (two RCTs each) out of a possible 16 points.

Fentanyl ITS compared with placebo (two RCTs, n=673): In the intervention group there were significantly lower rates of dropout due to inadequate analgesia (OR 0.32, 95% CI 0.23 to 0.45; two RCTs) and significantly lower pain scores (WMD -17.47mm, 95% CI -21.64 to -13.30; two RCTs).

Fentanyl ITS compared with morphine PCA (two RCTs, n=2,597): There was no statistically significant difference between the groups in pain relief or overall dropout rates. In the fentanyl ITS group the dropout rate due to inadequate analgesia was significantly higher (OR 2.01, 95% CI 1.47 to 2.74; four RCTs), but pain intensity scores at 24 hours were significantly lower (WMD -1.74mm, 95% CI -3.37, -0.12; four RCTs) and dropout rates due to adverse events were significantly lower (OR 0.66, 95% CI 0.46, 0.94; four RCTs).

Fixed-effect models were used throughout. Results for specific adverse events were reported in the review.

**Authors' conclusions**
The fentanyl ITS appeared safe and was more effective than placebo for acute postoperative analgesia. It was unclear whether fentanyl ITS was as effective as morphine PCA.

**CRD commentary**
The objectives of the review were clear and relevant sources were searched for studies without limitation by language. The restriction of the review to published studies meant that it could have been subject to publication bias; the authors acknowledged the potential for this, but it was not formally assessed. Steps were taken to minimise risk of reviewer bias and error by having more than one reviewer independently assess study validity. However, initial study selection was undertaken by a single reviewer and the process used for data extraction was not described. Few details were provided about characteristics of individual studies (such as participant age and gender). No information was provided about validity of individual studies, other than summary scores. These factors made it difficult to assess the reliability and applicability of the evidence presented. Appropriate statistical techniques were used to combine data and test for heterogeneity. However, no interpretation or cut-off value for $\chi^2$ or $I^2$ test results was provided, even though $I^2$ values on some forest plots were relatively high (up to 61%). In view of potential publication bias and poor reporting of study characteristics, study quality and review methods, the authors' conclusions may require cautious interpretation.

**Implications of the review for practice and research**
**Practice**: The authors stated that patients who used fentanyl ITS may have an increased need for breakthrough medication. They also noted that fentanyl ITS had been withdrawn from the market since September 2008 due to faults detected in one batch.

**Research**: The authors stated that future studies should investigate high dropout rates from inadequate analgesia associated with fentanyl ITS and whether such effects were time-dependant.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.