Prevention of pain on injection of propofol: systematic review and meta-analysis

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CRD summary
The review concluded that opioids should be used as standard pre treatment for preventing pain on injection of propofol, using an antecubital vein instead of a hand vein. Although the review was generally well-conducted, a lack of exploration of the possible causes of varying trial results suggests the authors' conclusions should be interpreted with a degree of caution.

Authors' objectives
To determine the most efficacious interventions for preventing pain on injection of propofol.

Searching
PubMed, EMBASE and The Cochrane Library were searched to December 2010 without language restrictions; search terms were reported. Reference lists of relevant papers and ClinicalTrials.gov were searched.

Study selection
Randomised controlled trials (RCTs) that compared the use of any drug or non-drug intervention (or a combination) with an active or inactive control and reported the response rate and severity of pain in adults who received intravenous propofol were eligible. The primary outcome was pain response rate.

A broad range of interventions was studied; lidocaine, non-steroidal anti-inflammatory drugs (NSAIDs), ketamine and opioids were most common. Comparator treatments commonly included no pre-treatment. Most patients were of categories one or two of the American Society of Anesthesiologists physical status classification system. Most patients were having elective surgery.

Two reviewers selected studies for inclusion; uncertainties were resolved by a third reviewer.

Assessment of study quality
Study quality was evaluated using the criteria: adequate sequence generation; adequate concealment of allocation; adequate blinding; and completeness of reporting data on outcomes. For each criterion studies were graded as having an unclear, high or low risk of bias.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted by one reviewer and checked by another. Relative risks (RR) and 95% confidence intervals (CI) were calculated.

Methods of synthesis
Pair-wise meta-analyses and indirect comparisons were used to pool data using a random-effects model. Only interventions that significantly reduced pain with a direct intervention comparison and with six or more included studies were included in the indirect comparison. Meta-regressions were conducted and a sensitivity analysis examined the effects of study quality criteria. Heterogeneity was assessed using \( \chi^2 \) tests and the \( I^2 \) statistic. Publication bias was assessed using funnel plots.

Results of the review
The review included 177 RCTs (n=25,260, range 24 to 388 participants). A low risk of bias was found for adequate sequence generation in 40% of included studies (n=71), adequate allocation concealment in 43% (n=76), blinding in 85% (n=151) and for whether incomplete outcome data were addressed in 88% (n=156).
Using an antecubital vein instead of a hand vein was the most effective single intervention (RR 0.14, 95% CI 0.07 to 0.30, I²=18%; six RCTs). Pre-treatment using lidocaine in conjunction with venous occlusion was also effective (RR 0.29, 0.22 to 0.38, I²=59%; 14 RCTs). Other significantly effective treatments included: a lidocaine-propofol admixture (25 RCTs); pre-treatment with lidocaine (24 RCTs), opioids (22 RCTs), ketamine (seven RCTs) or NSAIDs (seven RCTs); and propofol emulsions that contained medium- and long-chain triglycerides (24 RCTs). There was evidence of significant heterogeneity for some analyses. The funnel plot for the lidocaine-propofol admixture analysis indicated a strong possibility of publication bias. Sensitivity analyses that assessed study quality criteria yielded similar results to the main analyses.

Results of indirect comparisons showed that use of the antecubital vein and pre-treatment with lidocaine plus venous occlusion were significantly more effective than the other interventions.

**Authors' conclusions**

Unless contraindicated otherwise, it seems reasonable to use opioids as standard pre-treatment several minutes before induction, using an antecubital vein instead of a hand vein.

**CRD commentary**

The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify all relevant studies in any language were undertaken by searching electronic databases and checking references. Suitable methods were employed to reduce the risks of reviewer error and bias for the processes of data extraction and study selection; the authors did not report whether such methods were used for assessment of study quality. Sufficient study details were provided and study quality was adequately assessed, and results were used in interpreting the results of the review. Appropriate methods were used to pool data and assess heterogeneity. However, some analyses were subject to significant heterogeneity and the possible causes were not explored, which raised uncertainty regarding the reliability and generalisability of some results.

Although the review was generally well-conducted, the limited exploration of heterogeneity suggests the authors' conclusions should be interpreted with a degree of caution.

**Implications of the review for practice and research**

**Practice**: The authors stated that, unless contraindicated otherwise, it seemed reasonable to use opioids as standard pre-treatment several minutes before induction and use an antecubital vein instead of a hand vein. If the hand vein was the site of injection, they recommended pre-treatment using lidocaine in conjunction with venous occlusion or a combined intervention such as pre-treatment with ketamine or lidocaine before injection of a propofol emulsion that contained medium- and long-chain triglycerides. The authors presented a flow diagram of possible strategies.

**Research**: The authors stated a need for trials to clarify the results for interventions where small numbers of studies indicated statistically significant improvements.

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