Weak evidence that oral midazolam is an effective sedative agent for children undergoing dental treatment

Abstracted from

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Sedation of children undergoing dental treatment.

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Question: Which sedative agents are effective for behaviour management in children who are receiving dental care in order to allow completion of dental treatment?

Data sources Medline, Embase, Cochrane Central Register of Controlled Trials, Dissertation Abstracts, SIGLE, the WorldWideWeb (Google) and the Community of Science Database were searched for relevant trials and references. Reference lists from relevant articles were scanned and the authors contacted to identify trials and obtain additional information. There were no language restrictions. Trials pre-1966 were not searched.

Study selection Studies were included if they were randomised controlled trials of conscious sedation comparing two or more drugs/techniques/placebo undertaken by the dentist or one of the dental team in children up to 16 years of age.

Data extraction and synthesis Reference lists from relevant articles were scanned and the authors contacted to identify trials and obtain additional information. There were no language restrictions. Trials pre-1966 were not searched.

Results Thirty-six studies (2810 participants) were included. The majority of the trials (30) were of high risk of bias, the other six trials were at unclear risk of bias. Twenty-eight different sedatives were used with or without inhalational nitrous oxide, and the dosages, mode and timing of administration varied greatly. The trials were grouped into placebo-controlled, dosage and head-to-head comparisons. Meta-analysis was possible for studies investigating oral midazolam vs placebo only. There is weak evidence from five trials at high risk of bias, that the use of oral midazolam in doses between 0.25 mg/kg to 0.75 mg/kg is associated with more co-operative behaviour compared to placebo; standardised mean difference (SMD) favoured midazolam (SMD 2.98, 95% CI 1.58 to 4.37, $P < 0.001$, $I^2 = 91\%$). There was also very weak evidence from two trials which could not be pooled that inhalational nitrous oxide is more effective than placebo.

Conclusions There is some weak evidence that oral midazolam is an effective sedative agent for children undergoing dental treatment.

There is very weak evidence that nitrous oxide inhalation may also be effective. There is a need for further well designed and well reported clinical trials to evaluate other potential sedation agents. Further recommendations for future research are described and it is suggested that future trials evaluate experimental regimens in comparison with oral midazolam or inhaled nitrous oxide.

Commentary

As an update to a previous systematic review, this Cochrane review examines which sedation agents and dosages effectively manage behaviour for paediatric patients during dental procedures. The previous Cochrane review was unable to make any definitive conclusions based on the enormous complexity in aggregating the results from sedation studies that compare various agents and use numerous outcome measurements. For this updated review the authors were able to aggregate five studies and quantitatively estimate that oral midazolam has a net benefit in managing the behaviour of paediatric subjects.

The design of each of the aggregated studies was made admirably simple by including a comparison of at least one oral sedative agent versus a placebo and using a behaviour scale as an outcome measurement. Several limitations to these studies exist. First, the risk for bias remains unclear or low for each study. Second, one study included in the meta-analyses had 'transposed' tabular data that was corrected by the review authors.

Unsuccessful attempts were made to contact the original authors in order to verify the contradiction between the manuscript text and the transposed tabular data. The authors' analysis of heterogeneity showed that the pooled studies were still quite different in design. One concerning example is that some of these studies delivered the oral solution with IV formulated midazolam.

In fact, one study delivered 'oral' midazolam incrementally to augment the transmucosal absorption of midazolam, which is an inherently different sedative route. Overall, all of these issues reduce the strength of the pooled meta-analysis. Although the review authors appropriately used a random-effects method for meta-analysis to address heterogeneity, the conclusion that 'oral' midazolam has a net benefit in improving patient behaviour during dental treatment is quite weak.

Readers of this systematic review are cautioned to not misinterpret that oral midazolam has any superior outcomes versus any

This paper is based on a Cochrane Review published in the Cochrane Library 2012, issue 3 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Library should be consulted for the most recent version of the review.

other sedative agents. No definitive conclusion could be made between oral midazolam and other sedation agents.

This systematic review examined patient behaviour as the main criterion for comparison. Unfortunately, a systematic review of safety was not possible, and the reader should not assume a drug's suitability for use as a paediatric sedative based on a lack of data regarding negative outcomes.

Like most Cochrane systematic reviews, the authors urge more randomised controlled studies with stringent measures to reduce outcome bias. To those who will use this review as a guide for a future clinical trial, that remains a huge undertaking.

Practice points

- No conclusions can be made regarding which sedatives provide superior outcomes for behaviour.
- Evidence that oral midazolam improves behaviour is quite weak.

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