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Title:
Limited evidence for anti-inflammatory medications for obstructive sleep apnoea in children

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What is the review about?

The efficacy and safety of anti-inflammatory drugs for the treatment of obstructive sleep apnoea (OSA) in children.

What are the findings?

- There is insufficient evidence for the efficacy of intranasal corticosteroids for the treatment of OSA in children
- Montelukast has short term beneficial treatment effects for OSA in otherwise healthy, non-obese, surgically untreated children in terms of reducing the number of apnoeas, hypopnoeas and respiratory arousals during sleep, but the clinical relevance of the observed treatment effects remains unclear.

What are the findings based on?

Five randomised controlled trials (RCTs) comparing anti-inflammatory drugs against placebo in children between one and 16 years with objectively diagnosed OSA were included. RCTs were identified for intranasal corticosteroids (one each for fluticasone[2], budesonide[3]and mometasone[4]) and oral montelukast (4 or 5mg depending on the child's age)[5, 6], but no other anti-inflammatory medications.

Study characteristics
Trials with participants with major comorbidities were excluded, including morbid obesity. Eligibility for inclusion in each trial was based on the presence of OSA diagnosed using standard multi-channel physiological recordings (polysomnography). Severity of OSA was determined by the apnoea-hypopnoea index (AHI), the average frequency of obstructive apnoeas and hypopnoeas per hour of sleep time, and the presence of OSA for eligibility purposes was defined by an AHI of ≥1/hour(h). Treatment was for six to 16 weeks. The number of participants in each trial ranged from 25 to 62. The primary outcomes were the AHI and serious adverse events, and secondary outcomes included other measures of severity of OSA on polysomnography, including frequency of arousals from sleep related to obstructive events and measures of desaturation, clinical symptom scores, tonsil size and less serious adverse events. The avoidance of surgical treatment for OSA (usually adenotonsillectomy) was listed as a primary outcome in one study but the results for this outcome were not reported[6].

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Outcomes
One RCT of intranasal corticosteroid (budesonide[3]) was excluded from meta-analysis due to concerns about the analysis methods. The other two trials of intranasal corticosteroids showed a reduction in the AHI compared with placebo but this was not statistically significant (mean difference -3.18/h, 95% CI −8.70 to 2.35; 2 studies, 75 participants) (Figure 1). The secondary outcomes of frequency of arousals from sleep related to respiratory events, the mean SpO_2, tonsillar size and symptom score were slightly reduced (but again not statistically significant). There were also small improvements in the frequency of desaturation and the nadir SpO_2. Adverse events reported were minor and infrequent and were similar between the intervention and placebo groups.

In the two trials of montelukast, the AHI was significantly lower in the intervention group compared to placebo (mean difference −3.41 per hour (95% CI −5.36 to −1.45; 2 studies, 103 participants) (Figure 2). The respiratory arousal index, SpO_2 nadir and frequency of desaturation also improved (but was statistically significant only for the respiratory arousal index). The difference in change in mean SpO_2 and tonsillar size was uncertain, and improvement in symptoms was not reported in this review although was reported in Goldbart et al[5]. One study reported no adverse events[5]; while the other reported minor adverse events at a similar frequency between the intervention and control groups[6].

Evidence certainty
Certainty of the evidence was analysed by GRADE Working Group classification which considers risk of bias, consistency of effect, imprecision, indirectness and publication bias. The certainty of the evidence for corticosteroid nasal spray for the treatment of OSA was low for the primary outcome due to imprecision (confidence intervals of the pooled estimate of the treatment effect included the null) and inconsistency between the two included studies. The evidence for the use of montelukast was of moderate certainty for the primary outcome. Adequacy of allocation concealment and blinding was unclear for one of the montelukast studies[6] and there was some inconsistency of the effect between the two included studies.

Implications for practice

- It is uncertain if intranasal corticosteroids improve outcomes for children with OSA.
- Montelukast has a short-term beneficial effect for the treatment of OSA in otherwise healthy, non-obese, surgically untreated children with OSA but there is insufficient evidence to recommend use as a first line treatment given the potential for side effects.

Clinical perspective

This meta-analysis did not find evidence of efficacy of intranasal corticosteroids for the treatment of OSA due to imprecision of the treatment effect and considerable heterogeneity between studies. Despite some encouraging positive findings in cohort studies and small RCTs of intranasal steroids for OSA[2, 4, 7], the results of this meta-analysis mean that we are not at the point of being able to recommend intranasal corticosteroids for all children with mild to moderate OSA.

There is emerging evidence of efficacy of montelukast for short-term benefit in severity of OSA, but a small magnitude of improvement. As such, the clinical relevance remains unclear.

The modest impact of montelukast also needs to be balanced with the known risk of adverse neuropsychiatric side effects[8].

This Cochrane review updates the 2011 one that included only three trials[9]. The authors call for further research, highlighting how common OSA is in children (1% to 4% of children) and its adverse impacts, particularly on behaviour and learning[10]. There are additional important questions that require future research, particularly the question of the efficacy of these agents for the larger group of children with symptoms of obstructed breathing during sleep who have not undergone polysomnography (estimated at 10%[11]). Limited availability of polysomnography means that treatment decisions for most children are made on the basis of clinical assessment alone, despite guidelines recommending polysomography[10, 12]. In addition, key patient-centred outcomes such as improvement in behaviour and quality of life were not addressed in the studies included, and the impact on symptoms was uncertain. The duration of any benefit, and whether it is enough to avoid surgery, are also of critical importance. Small improvements in AHI may be clinically significant as measured by polysomnography, but if they are not accompanied by an improvement in symptoms sufficient to improve quality of life and alleviate parental concern, then they will not translate to improved health outcomes and reduced health service contact.

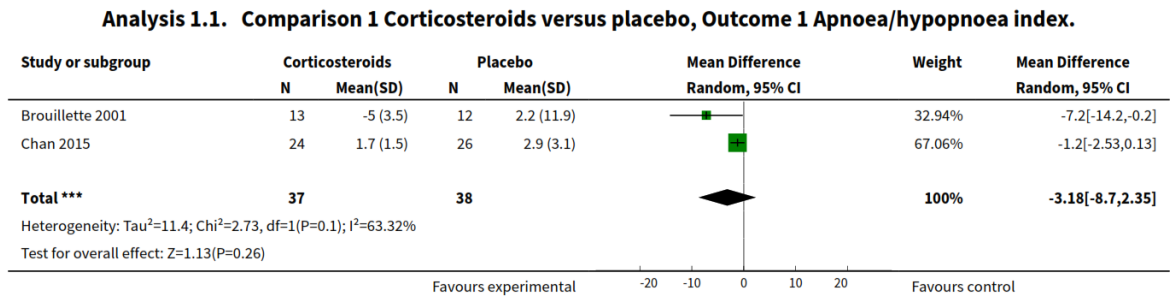

Figure 1. Forest plot for the primary outcome of apnoea hypopnoea index (AHI) in trials of intranasal corticosteroid.

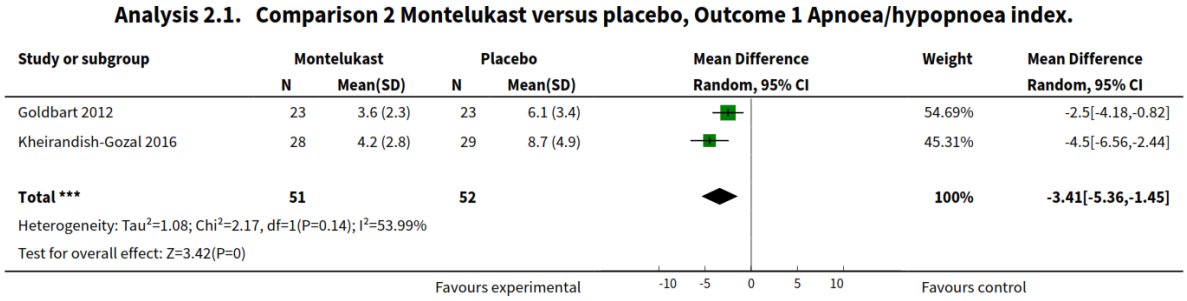

Figure 2. Forest plot for the primary outcome of apnoea hypopnoea index (AHI) in trials of montelukast.

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COCHRANE COMMENTARIES

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