

Enhancing the Management of Acute Asthma in Children: Do We Have the Evidence?

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Some months back, Indian Journal of Pediatrics suggested ways to enhance the management of persistent asthma in children, to improve outcomes [1]. This issue of the Journal includes two well-designed studies [2, 3], exploring the potential for improving the management (and outcomes) of acute asthma. Arulparithi et al. describe a randomized trial comparing the efficacy of inhaled Budesonide vs. oral Prednisolone in a small cohort of children with mild to moderate severity acute asthma [2]; and Wang et al. investigated the efficacy of inhaled magnesium on provoked bronchospasm in another cohort of children [3].

The possibility of using inhaled corticosteroids (ICS) for acute asthma intrigued researchers almost since systemic corticosteroid (SCS) use became routine practice. Some initial trials compared the addition of ICS to SCS vs. SCS alone. One of the earliest trials comparing ICS directly against SCS in children [4] was conducted in this institution and reported that three doses of budesonide resulted in better clinical score, oxygen saturation, respiratory rate, and overall clinical improvement (reflected by fitness for discharge) compared to those who received oral prednisolone. Systematic reviews over the past decade have suggested (but not proven) benefits of ICS used alone or in combination with SCS in acute asthma. It is interesting to note that one group of authors have published five Cochrane reviews [5–9] on the subject. The first four, published annually from 2000 to 2003 [6–9] suggested decreased hospitalization with ICS vs. placebo; and ICS+SCS vs. SCS alone. However at that time, data comparing ICS vs. SCS head-to-head were insufficient for meta-analysis. Following a gap of nearly 10 years, the authors revisited the issue [5] reporting comparable hospitalization

rate with ICS vs. SCS (OR 0.56, 95 % CI 0.25, 1.24; 10 trials, 763 participants), suggesting some benefits of ICS, but insufficient evidence that it can replace SCS. Recent updated Asthma Management Guidelines also do not recommend using ICS in place of oral/systemic steroids in children with acute asthma [10–12].

Against this backdrop, what does the trial by Arulparithi [2] contribute? The investigators have designed the study almost exactly like the original trial published 15 y back [4]. Critical appraisal of trial validity confirms computer generated sequence for randomization, and appropriate allocation concealment using sealed opaque envelopes although these were picked at random. The double dummy design ensured blinding of participants but outcome assessor blinding is not described. Patients were followed-up for a maximum of four hours only and no outcomes were recorded beyond this. There was no attrition and data reporting is not selective or incomplete. Overall, this is consistent with moderate methodological quality.

The authors have chosen a relatively non-specific definition of asthma citing British Thoracic Society (BTS) Guidelines. But the authors' definition corresponds only to a "high probability of asthma" (and not diagnosis) as per the BTS Guideline [10]. This may or may not impact the trial results since the definitions for acute asthma and severe disease (inclusion and exclusion criteria) are acceptable. Further, what outcomes are relevant for such a trial in today's clinical setting? A decade back, such trials rightly focused on proof-of-concept outcomes (such as heart rate, respiratory rate, oxygenation, fitness-for-discharge *etc.*). However, current trials would be expected to report beyond such outcomes and focus on patient-centric (need for hospitalization, complication rate, stability after discharge, patient preference/convenience *etc.*) and health-care resource utilization (length of Emergency stay, re-admission after discharge, cost of therapy, *etc.*) outcomes. The investigators have missed the

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opportunity to examine such outcomes thereby limiting the trial to a replication of previous findings [4]. In other words, despite conducting a fairly well-designed trial, we are left with the tantalizing suggestion (but not definite proof) that ICS can replace SCS. On the brighter side, the data from this trial can be pooled with other trial data, contributing to another meta-analysis.

The other trial in this Journal explored an even more contentious issue *viz* the relationship between provoked bronchospasm and magnesium sulphate inhalation, in childhood asthma [3]. A recent Cochrane review comparing inhaled magnesium in addition to beta-2 agonist inhalation (*vs.* the latter alone) in acute asthma, reported comparable hospitalization rates (RR 0.76; 95 % CI 0.49, 1.16; 3 trials, 249 participants) and improvement in FEV1 (SMD 0.20; 95 % CI -0.09, 0.49; 3 trials, 188 participants) [13]. Limited data from children did not suggest any difference between the groups. A more recent randomized controlled trial [14] compared inhaled magnesium to intravenous magnesium and standard treatment in adult patients with severe acute asthma. Intravenous route resulted in a trend towards reduced hospitalization (OR 0.73, 95 % CI 0.51, 1.04), and improvement in patient-reported breathlessness (compared to placebo). However inhaled magnesium did not show similar benefit for hospitalization (OR 0.96, 95 % CI 0.65, 1.40) or breathlessness. These observations are in line with previous systematic reviews reporting some degree of benefit on lung function parameters [13, 15] but not on hospitalization. In contrast, data analysis in children did not show comparable benefits except in some with severe acute exacerbations [16]. Thus there is considerable uncertainty about the scope and place of inhaled magnesium in acute asthma.

In such a setting, Wang's trial focusing on the role of magnesium in bronchial reactivity provoked by acetylcholine, is more to explore and elucidate a potential role, rather than to change clinical practice [3]. The trial methodology used appropriate random sequence generation (by personnel not connected with the trial). Allocation concealment appears to have been done, but the method is not described. Blinding of participants, personnel and outcome assessors is not clearly mentioned, but suggested to have been done. There is no incomplete outcome data or selective outcome reporting. Follow-up was adequate and all patients were analysed in the groups to which they were randomised. All groups were treated equally, apart from the interventions being compared. The investigators evaluated clinical parameters relevant to the acute setting, rather than actual patient outcomes.

The data did not suggest any benefit of using magnesium alone or in combination with beta-2 agonist. Given that beta-2 agonists works very well to relieve bronchospasm (proven in this trial also), and the fact that the authors did not evaluate the frequency of beta-2 agonist related side effects, the purpose of undertaking a trial of this nature is unclear. Had magnesium

shown some benefit, it would be useful to determine whether beta-2 agonist dose and thereby potential adverse effects, could be reduced.

In summary, both trials provide food for thought, but neither provides a strong justification to consider change in current clinical practice [2, 3].

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