This yielded 38 hits, of which 8 articles were relevant. Articles were excluded if: they were letters/comments only; they were studies where the majority of patients were adults; the effect of BCG vaccine or TB meningitis was not directly examined, i.e. results not site specific.

See table 1.

Commentary

Neonatal BCG vaccination is established in the UK for at-risk groups. The papers we reviewed made widely ranging suggestions, from the recommendation that in low risk areas routine BCG ought not to be used,[6] to the comment that in some areas a second early childhood immunisation might be required to maintain immunity.[4] New recommendations for BCG vaccination in the UK have been published recently.[7]

The meta-analysis published in 1993[1] sought to differentiate between different sites of disease and the protective effect of BCG. This study, however, included a range of papers from the previous three decades (earliest 1953), and the inclusion criteria used were not robust, for example a paper labelled a randomised controlled trial was included which only considered two cases. Some of their evidence, we suspect, might not be included if a formal meta-analysis were performed using current standards. The meta-analysis conducted in 1995[8] was more substantial and aimed to quantify the efficacy of BCG and the duration of protective immunity.

Since this time there have been a number of case control studies concurring that neonatal BCG vaccination offers significant protection against TB.[2 3 5] Papers that draw the conclusion that there is poor protection from BCG immunisation against TBM are weak in design and method; this is upheld by Colditz meta-analysis.[7]

A number of queries were raised considering other factors which may influence BCG effectiveness. Children who were malnourished or underweight or of low socioeconomic status were deemed to have less protective effect from BCG.[2 5] It was also suggested that BCG loses its efficacy after a number of years. The 1995 meta-analysis concluded that BCG efficacy may persist 10 years after infant vaccination.

BCG vaccination does have a significant protective effect against tuberculous meningitis (75–87%). Therefore a history of vaccination and a BCG scar can afford a certain degree of reassurance when considering TBM in infants and young children. However, there have been questions raised about the duration of vaccine efficacy and therefore the effectiveness of BCG vaccination in older children. There will always be a proportion of children not protected by the vaccine they are given, including BCG. There is limited evidence to help determine whether a history of BCG vaccination and/or presence of a scar alters the likelihood of TBM. Indeed, it might be true that the BCG scar is a proxy marker for a higher risk of TB exposure. As always, each situation needs to be judged on clinical grounds. Although protective, it is clear that BCG vaccination is not 100% efficacious in preventing TBM.

CLINICAL BOTTOM LINE

- BCG vaccination is partially protective against tuberculosis meningitis; therefore a history of BCG vaccination or the presence of a BCG scar affords some degree of reassurance when considering TBM. (Grade C)
- Where TB meningitis is clinically suspected, the diagnosis needs to be rigorously investigated and a history of BCG does not rule out the diagnosis. (Grade C)

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Does dexamethasone reduce the risk of extubation failure in ventilated children?

Report by

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John, a 4 year old boy, has been mechanically ventilated for three days during recovery from a blunt chest trauma. According to his level of ventilator support, he is considered to be ready to be extubated. The previous patient had to be reintubated as a result of postextubation laryngeal oedema. You wonder whether corticosteroids may reduce this risk of extubation failure.

Structured clinical question

In mechanically ventilated children [patient] does corticosteroid administration [intervention] reduce the chance of reintubation due to laryngeal oedema [outcome]?

Search strategy and outcome

Secondary sources

Cochrane Database of Systematic Reviews; 1 limited to newborn infants.[1]

PubMed clinical queries

''Respiration, Artificial''[MESH] AND (Hydroxycorticosteroids) [MESH] AND systematic; 1 reference not related to the question.

(''Intubation, Intratracheal''[MeSH]) AND systematic[sb] AND (Hydroxycorticosteroids)[MESH]; no references.

PubMed

(Anti-Inflammatory Agents OR Anti-Inflammatory Agents/therapeutic use OR Anti-Inflammatory Agents/therapy OR hydroxycorticosteroids) AND systematic[sb]) AND (''Intubation, Intratracheal''[MeSH] OR ''Respiration, Artificial''[MeSH]); 25 references, 2 relevant studies[1 2] (table 2).

(''reintubation'' or (''failure'' and ''extubation'')) AND (Anti-Inflammatory Agents OR Anti-Inflammatory Agents/therapeutic use OR Anti-Inflammatory Agents/therapy OR hydroxycorticosteroids); 30 references, with 4 relevant.[3–6]

Table 2 Dexamethasone in ventilated children

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Davis and Henderson-Smart (2001)[1]	3 randomised controlled trials (RCTs) addressing the effects of treatment with dexamethasone to facilitate extubation of newborn infants. n=160, reintubation treatment group 12/119, control group 16/120	Systematic review (level 1a)	Need for endotracheal intubation	Neonates overall: RRR 87% (95% CI 17 to 100%), ARR 0.09 (95% CI 0.02 to 0.16). NNT 11 (95% CI 6 to 60) Neonates, high-risk group: RRR 100% (95% CI −39 to 100%), ARR 0.17 (95% CI 0.02 to 0.33). NNT 6 (95% CI 3 to 52)	Study limited to neonates. Reintubation rate as a result of laryngeal oedema alone not clearly stated
Markovitz and Randolph (2002)[7]	Six RCTs, five of which on the use of steroids for the prevention of reintubation in children and/or neonates. One paediatric study on children with previous failed intubation was excluded[3] Neonates: n=160, reintubation treatment group 1/80, control group 4/80. Children: n=216, reintubation treatment group 9/107, control group 11/107	Systematic review (level 1a)	Need for endotracheal intubation	Neonates: RRR 87% (95% CI 17 to 100%), ARR 0.09 (95% CI 0.02 to 0.16). NNT 11 (95% CI 6 to 60) Children (overall): RRR 17% (95% CI −60 to 93%), ARR 0.02 (95% CI −0.06 to 0.09)	Heterogeneity between studies on dose-regimen, inclusion criteria and outcome
Meade *et al* (2001)[2]	Three RCTs that addressed whether pre-extubation steroid administration reduces post-extubation complications in children, including one study on children with previous failed intubation[3]. n=239, reintubation treatment group 12/119, control group 16/120	Systematic review (level 1a)	Need for endotracheal intubation	Children overall: RRR 24% (95% CI −37 to 85%), ARR 0.03 (95% CI −0.05 to 0.11) Children, high-risk group: RRR 45% (95% CI −39 to 100%), ARR 0.20 (95% CI −0.18 to 0.59)	Randomisation not clearly stated in two trials, two trials limited to primary extubation. Heterogeneity between studies on dose-regimen, inclusion criteria and outcome

''reintub*'' AND ''steroids''; 30 references, 7 relevant,[1–7] of which 1 systematic review[7] (table 2), 4 studies[3–6] had been analysed in systematic reviews[1 2] and were not included in table 2.

Commentary

The outcome, requirement for endotracheal reintubation, is of clinical importance in the spectrum of those relating to paediatric intensive care. Paediatric intensive care patients with failed intubation have longer hospital, paediatric intensive care, and ventilator courses, leading to additional costs, risks, and patient burden. The risk of reintubation in this patient group is above 10%.[2–4]

In the ex-preterm intubated newborn, prophylactic corticosteroids reduce the need for reintubation. In the paediatric population, the benefit of prophylaxis is less clear. The overall benefit is estimated at 1 in 59 children succeeding extubation when they would have failed without corticosteroid prophylaxis. However, the study size means that the true value may be that as few as 11 children need to be treated, or indeed that treating 17 children causes one an additional failure that would not have occurred if a placebo had been given. Limiting prophylaxis to children at risk for developing post-extubation laryngeal oedema (e.g. multiple airway manipulations, or failed prior extubation), the benefit seems to improve. In this patient group, five children (95% CI 3 to 13) have to be treated to avoid one reintubation.

Dexamethasone is a potent glucocorticoid with many effects beyond reducing airway oedema. The disturbance to glucose metabolism is well demonstrated,[5] although the clinical relevance has yet to be shown. Prophylactic use of dexamethasone was not associated with the development of hypertension in neonates.[1 5] Anene *et al* noted one patient treated with gastrointestinal bleeding.[4] The drug is not without side effects and defining the group of children in whom it is most likely to be effective seems desirable, since the trend towards a favourable effect of prophylaxis is most expressed in this group. The studies had relatively few patients, and showed significant heterogeneity. As a result the power of the data is limited. Furthermore, the dose regimen varied between the studies, varying from a single low dose immediately prior to extubation to multiple high doses given 24 hours prior to extubation.

A well designed, adequately powered prospective study limited to patients at risk for extubation failure, to assess the benefits and side effects of prophylactic steroid treatment in this group of paediatric patients is warranted to draw firm conclusions. Awaiting such a trial one could argue that, given the impact of endotracheal reintubation, the costs associated with failed extubation, the relative low costs of accepting a significant NNT, and the absence of clinical significant side effects, prophylactic multiple dose corticosteroid administration prior to extubation in high risk neonatal and paediatric patients can be defended. Given the lack of effect in low risk patients and potential side effects, it seems reasonable to withhold steroid prophylaxis in these patients.

CLINICAL BOTTOM LINE

- Extubation failure in children, due to post-extubation laryngeal oedema occurs in about 10% of patients. (Grade B)
- Steroid prophylaxis reduces reintubation rate in high risk neonates and children (e.g. children with multiple airway manipulations) receiving multiple dose dexamethasone. (Grade B)
- Steroid prophylaxis does not reduce extubation failure in low risk paediatric patients. (Grade B)

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Should metformin be prescribed to overweight adolescents in whom dietary/behavioural modifications have not helped?

Report by

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An obese, 12 year old girl comes for review in clinic. A year ago when you first saw her you gave comprehensive advice regarding dietary modification, and exercise. She has continued to gain weight with a BMI greater than the 99th centile. You arrange for an oral glucose tolerance test to be performed which shows her to be hyperinsulinaemic with fasting insulin of 20 mIU/l, and 120 min insulin of 200 mIU/l. She has normal fasting and 120 min blood glucose measurements. You wonder whether prescribing metformin may help her to lose weight.

Structured clinical question

In obese hyperinsulinaemic adolescents [patient] is metformin [intervention] effective in promoting weight loss [outcome]?

Search strategy and outcome

Secondary (Cochrane library, 2004) and primary (Medline, Embase) sources were included in the search.

Search strategy: ''Obesity'' AND ''Adolescent'' AND ''Metformin''.

Search outcome: 276 hits (14; 61; 201; each search respectively), of which 2 (2; 2; 0) studies were directly relevant to this question.

See table 3.

Commentary

Child and adolescent obesity is a significant and growing health problem frequently encountered in general paediatric clinics, with recent data having shown that obesity in childhood and adolescence increases cardiovascular mortality in adulthood.[1]

Clinical approaches to childhood obesity have concentrated on diet and exercise programmes, and the benefit of drug treatment for the severely obese remains largely untested. This is particularly an issue during adolescence, when puberty induces reduced insulin sensitivity,[2] the development of sexually dimorphic patterns in blood pressure[3] and lipids,[4] and increased deposition of visceral fat.[5] Obesity in childhood has been shown to increase the risk of the insulin resistance syndrome (consisting of obesity, hypertension, dyslipidaemia, and atherosclerosis, leading to increased risk of cardiovascular disease in adult life), with one third of obese children and adolescents having been shown to have the insulin resistance syndrome.[6 7]

Metformin, a biguanide, offers significant potential to intervene to reduce or reverse the metabolic and endocrine changes associated with obesity during puberty. Metformin acts by suppression of endogenous glucose production in the liver, but may also have an insulin sensitising effect in peripheral tissues through an effect on the key intracellular enzyme AMP kinase.[8]

Metformin has been shown to reduce weight as well as reducing hyperinsulinaemia and hyperglycaemia in type 2 diabetes in adults.[9] Similar benefits on hyperinsulinaemia and BMI have been reported in non-diabetic obese adults,[10 11] in addition to a reduction in progression from impaired glucose tolerance to frank diabetes.[12] In women with polycystic ovarian syndrome (PCOS), metformin has been shown to reduce hyperandrogenaemia and reduce total cholesterol as well as improving symptoms.[13] There is also very early evidence that metformin may reduce the risk of cancer associated with obesity in adults with type 2 diabetes, possibly through activation of the tumour suppressor protein kinase LKB1.[14]

We looked at research in to whether pharmacological approaches may be most appropriate for very obese hyperinsulinaemic adolescents (approximately 2–3% of early adolescents of both sexes have BMI $\geq$+3 SD[15]).

We found two small short term randomised controlled trials that specifically answered our question. In the first, an eight week placebo controlled randomised trial in 24 obese hyperinsulinaemic non-diabetic 13–17 year adolescents, Kay

Table 3 Metformin in overweight adolescents

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Kay *et al* (2001)[16]	24 hyperinsulinaemic non-diabetic obese 13–17 year adolescents Randomised to metformin or placebo	8 week randomised placebo controlled trial (level 1b)	Weight reduction (measured in kg)	Metformin group had a greater weight loss (kg) (6.5% [plus/mn] 0.8% v 3.8 [plus/mn] 0.4% p=0.01, greater decrease in body fat (p=0.01)	Metformin (850 mg BD for 8 weeks) Small study Subjects only followed up for brief time—8 wk
Freemark *et al* (2001)[17]	29 obese hyperinsulinaemic non-diabetic 12–19 year olds with a BMI >30 kg/m^2 Randomised to metformin or placebo	6 mth randomised placebo controlled trial (level 1b)	Reduction in BMI	Metformin caused a decline of 0.12 standard deviations (BMI) in study participants (−1.3%) compared with a rise of 0.23 SD in placebo controls	Metformin 1 g/day for 6 mth Small study