Towards evidence based medicine for paediatricians

Edited by Bob Phillips

Randomisation

Randomisation is used within the context of therapeutic studies to try to reduce bias. It does this by using chance to spread, hopefully evenly, important prognostic factors across the groups within the study.

Randomisation can be performed in a number of ways; each variation can be used in different trial situations. To make life easier, for this article we’ll assume there are just two arms, but the principles apply to studies with greater numbers of options too. Simple randomisation is as straightforward as tossing a coin for each individual entered. In small studies, doing this may run the risk of having an uneven number of participants in the trial arms, making interpretation more difficult. The simplest variation on this is to predetermine the number of individuals in the study, and (metaphorically) put the appropriate number of “A”s and “B”s in a bag and withdraw the letters. This gives an even spread of numbers across the study arms—but is impossible to achieve for very large studies.

Block randomisation is where a block of participants (typically 6–12 in size) is randomised into an even split between “A”s and “B”s. This lets “time” be balanced between the arms—e.g., winter versus spring admissions—and balances the workload between the arms—if the treatments are not drug therapies but physiotherapy, surgery, or a multidisciplinary team intervention. It also allows a study to stop with an even spread between the arms. However, if the blocks are of the same size it may be possible for investigators to start to guess what’s coming next, upsetting the allocation concealment and jeopardising the trial.1 One way around this is taking blocks of 6, 8, and 10 participants and randomising the order of these too.

Stratified randomisation is a method where the investigator doesn’t leave the distribution of known or presumed prognostic variables entirely to chance; instead each major variable (for example, age, tumour stage, biological marker) is treated almost as a separate mini-trial, and participants within these strata are randomised independent of the other strata. (As a rule of thumb, you need at least 10 participants in each arm to make this valuable.) A similar type of process is used in minimisation allocation, which achieves similar results by a slightly different method.

Finally, cluster randomisation should be used when the unit randomised is not an individual child or family, but institution or group. For example, a trial of providing mosquito netting to prevent malaria may randomise villages, a study of a new computerised decision support system may randomise family practices.

Reference


REFERENCES

Should steroids be used in children with meningococcal shock?

Report by
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doi: 10.1136/adc.2005.077701

A 3 year old boy is admitted to a paediatric intensive care unit with a history of fever, non-blanching petechial rash, decreased conscious level, and grunting; capillary refill is poor. After screening for sepsis, antibiotics are started. He is intubated, receives fluid resuscitation (total of 100 ml/kg), and a central catheter is placed, showing a central venous pressure of 12 mm Hg. Despite dopamine infusion, the attending physician is unable to stabilise his blood pressure, and he requires noradrenaline infusion to achieve and maintain his haemodynamic state.

Structured clinical question
In a child with meningococcal shock [patient group] does steroid replacement therapy [intervention] decrease mortality [outcome]? 

Table 1: Randomised controlled trials testing the use of steroids in low dose for septic shock

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane et al (2002)</td>
<td>300 adults with dopamine resistant septic shock divided according to the increase in cortisol in response to short corticotropin test (250 µg) as responders (≥9 µg/dl) or non-responders (&lt;9 µg/dl)</td>
<td>Randomised controlled trial (hydrocortisone 200 mg/day + fludrocortisone 50 µg/day v placebo, for 7 days)</td>
<td>28 day survival</td>
<td>Time to vasopressor withdraw</td>
<td>28 day mortality of (steroids v placebo) 60/114 v 73/115 in the non-responders and 22/36 v 18/34 for responders-adjusted Odds ratios of 0.54 (0.31–0.97) and 0.97 (0.32–2.97), respectively</td>
</tr>
<tr>
<td>Bollaert et al (1998)</td>
<td>41 adults with septic shock requiring catecholamine for more than 48 hours Response to corticotrophin stimulation test (increase &gt;6 µg/dl)</td>
<td>Randomised controlled trial (300 mg/day hydrocortisone v placebo, for &gt;5 days)</td>
<td>7 day reversal of shock</td>
<td>28 day mortality</td>
<td>7 day reversal of shock (15/22 v 4/19, p = 0.007) Similar improve (7 d, 28 m) in responder and non-responder</td>
</tr>
<tr>
<td>Yildiz et al (2002)</td>
<td>40 adults with sepsis</td>
<td>Randomised controlled trial (prednisolone 7.5 mg/day, for 10 days)</td>
<td>28 day mortality</td>
<td>8/20 steroid and 12/20 placebo (p = 0.34)</td>
<td>Higher difference in APACHE II (&gt;20 not calculated)</td>
</tr>
</tbody>
</table>

Search strategy and outcome
Secondary (Cochrane library, 2004) and primary (Medline, Embase, Scielo) sources were included in the search. MeSH terms were used in Medline and Embase.

Search strategies: “meningococcal” AND “steroid replacement”; “meningococcal” AND “steroids” (limited to “all children” from 1984 to 2004); “shock, septic” AND “steroids” (limited to “randomised controlled trials” from 1992 to 2004).

Search outcome: 68 hits (3; 52; 13; each search respectively), of which 6 (0; 3; 3) studies were directly relevant to the question. See tables 1 and 2.

Commentary
The use of steroids in septic shock has been discussed for decades. The use of high dose steroids (30 mg/kg of methylprednisolone or equivalent) for a short period has been proven not to improve outcome. However, the use of low doses (200–300 mg of hydrocortisone in adults; around 2–5 mg/kg/day in children) for longer periods (replacement therapy) has shown very promising results in adults. 2–4 Table 1 summarises the main randomised controlled trials testing the use of steroids in low dose for septic shock. Although there is a discrepancy in the populations (and on the criteria for adrenal insufficiency), replacement therapy with steroids showed either significant reduction in the duration of inotrope requirement and 28 day mortality, or a tendency towards improvement. Although no studies have evaluated the use of steroids in paediatric septic shock, expert opinion (for example, the Society of Critical Care Medicine clinical practice parameters) recommends the use of hydrocortisone in children with septic shock requiring catecholamines for blood pressure support and adrenal insufficiency, as evidenced by total cortisol lower than 18 mg/dl.

Meningococcal septic shock presents with an early, massive inflammatory response. Although absolute adrenal failure due to adrenal haemorrhage is rare, partial adrenal insufficiency has been described in these children even in the absence of adrenal haemorrhage.5–7 Table 2 summarises the main studies that have evaluated adrenal function in children with meningococcal disease. The incidence of adrenal insufficiency varied from 10.3% to 16.9% in children with...
shock. Of note, children with very severe disease had lower cortisol levels than children with a moderate presentation.\(^5\)–\(^7\) Moreover, after a low dose Synacthen test, cortisol levels did not increase as much in the more severely affected children than children with a moderate presentation.\(^5\)–\(^7\)

In summary, children with meningococcal shock have increased incidence of abnormal adrenal response, and extrapolation of data from adult septic shock and expert opinion supports the use of hydrocortisone replacement therapy in children with meningococcal shock dependent on catecholamines.

**REFERENCES**


This case is based on experience from several cases. Details have been altered to ensure patient anonymity.

**Should children with Henoch-Schönlein purpura and abdominal pain be treated with steroids?**

**Report by**

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doi: 10.1136/adc.2005.077743

Hannah is a 7 year old girl with Henoch-Schönlein purpura (HSP). She has a lot of abdominal pain which is not settling with simple analgesia. An ultrasound scan reveals that she does not have an intussusception. The SHO on-call tells you that her handbook of paediatrics says that such pain can be treated with steroids, but is there really any evidence to support this?

**Structured clinical question**

Do children with abdominal pain and HSP [population] treated with steroids [intervention] compared to children treated without steroids [comparison] show a more rapid resolution to their symptoms [outcome]?
Search strategy and outcome
Secondary sources
Best Bets: “Henoch Schonlein purpura”; match all/any words. No relevant citations.
“Steroids abdominal pain”; match all words. No relevant citations.
Match any words; 125 hits, no relevant citations.
Cochrane: “henoch schonlein purpura” (MeSH); 11 hits. None relevant.
“steroids” and “abdominal pain”; 43 hits. None relevant.

Primary source
Medline 1966–2004:
“Henoch Schonlein Purpura” AND “steroids” AND abdominal pain; 21 citations; 2 relevant.
“Henoch Schonlein Purpura” AND “abdominal pain”; 169 citations; no further relevant citations.
“Henoch schonlein purpura” AND (“steroids” OR “prednisolone” OR “hydrocortisone” OR “dexamethasone”) AND “pain”; 26 citations; 5 relevant.
See table 3.

Commentary
Henoch-Schonlein purpura is the most common vasculitic disease in childhood, most commonly affecting the skin, joints, gastrointestinal tract, and kidneys. Gastrointestinal involvement is said to occur in approximately 80% of patients, ranging from mild symptoms such as abdominal pain, nausea, and vomiting, to more severe manifestations such as gastrointestinal bleeding and intussusception. Some textbooks suggest that the abdominal pain of HSP may respond to steroids, with some suggesting that there is a benefit in their use and describing a regimen.

No randomised controlled trials have ever been carried out to assess this problem and there have been no systematic reviews to date looking at the available data. The studies that are available include retrospective studies and case series. These studies show that children with HSP who are treated with steroids experience a quicker resolution of their pain than those not treated with steroids. This is seen within 24 hours of commencing treatment in the studies by Rosenblum and Reinehr et al.

Although the groups were similar for some characteristics, randomisation and blinding was not carried out—thus there is little to ensure that patients were equal in terms of factors such as severity of illness.

While steroids have been described in these studies as having a beneficial effect on abdominal pain, they are also known to have adverse effects, some of which have been noted in these studies—for instance, the masking of associated intra-abdominal pathology such as intussusceptions and bowel perforation.

A randomised controlled trial seems the natural next step in order to answer this question. If we assume that a trial looking at the effect of steroids for severe abdominal pain will have a power of 80% at a 5% significance level and assume 15% complete resolution of pain at 24 hours in placebo treated children and 25% resolution of pain in children treated children and 25% resolution of pain in children treated with steroids, with a power of 80% at a 5% significance level and assuming a 25% resolution in the placebo group, a sample size of 100 children per group would be required.

Table 3 Use of steroids in children with Henoch-Schonlein purpura and abdominal pain

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenblum (1987)²</td>
<td>Cohort 3b</td>
<td>43 patients with HSP and abdominal pain</td>
<td>Resolution of pain at: 24 h 44% v 14% p = 0.02; 48 h 65% v 45% p = NS; 72 h 78% v 76% p = NS</td>
<td>Similar groups but no mention of the use of analgesia in these groups.</td>
<td>No mention of length of follow-up, discharge/re-admission for pain.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 (58%) given prednisone; 18 (42%) not given prednisone</td>
<td>Steroid treated v non treated</td>
<td>Steroid treated v non treated</td>
<td>Limited details of group. Age and sex distribution.</td>
</tr>
<tr>
<td>Leung (2001)³</td>
<td>Case series 4</td>
<td>Case reports of 2 patients (both aged 5) with HSP and abdominal pain treated with intravenous hydrocortisone</td>
<td>Resolution of pain within 10 minutes</td>
<td>Rapid relief but pain relapse at later date. Little mention of conventional analgesia.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Steroid treated v non treated</td>
<td>Steroid treated v non treated</td>
<td>Limited data.</td>
</tr>
<tr>
<td>Lin et al (1998)⁴</td>
<td>Retrospective study 47</td>
<td>27 children (6.7 ± 0.5 y) with HSP and abdominal pain treated with corticosteroids</td>
<td>Resolution of pain in 2.4 ± 0.2 days</td>
<td>English abstract only. Limited data</td>
<td>No mention of length of follow-up. Discharge/re-admission for pain.</td>
</tr>
<tr>
<td>Reinehr et al (2000)⁵</td>
<td>Retrospective study 47</td>
<td>101 children (mean 6 y) with HSP, 57 with severe pain or bleeding treated with steroids</td>
<td>Resolution of pain</td>
<td>Steroid treated children: 77%—pain resolved in 24 h; Non-steroid treated persistent pain for 5 days (median), range 1–28 days</td>
<td>Steroid treated children: 77%—pain resolved in 24 h; Non-steroid treated persistent pain for 5 days (median), range 1–28 days</td>
</tr>
<tr>
<td>Gunasekaran et al (2000)⁶</td>
<td>Case series 23</td>
<td>4 children with confirmed duodenal jejunitis and clinical manifestations of HSP without the typical rash</td>
<td>Resolution of pain</td>
<td>Marked improvement in pain in 48 h Normal</td>
<td>Patients followed up for 3 years</td>
</tr>
<tr>
<td>Van den Broek et al (1999)⁷</td>
<td>Case report</td>
<td>4 year old with HSP treated with IV prednisone</td>
<td>Resolution of pain</td>
<td>Improvement in two days. Entero-enteral fistula and abscess.</td>
<td>Steroids started on day 7 of illness. Surgical complications diagnosed on day 25 at laparotomy after steroids stopped on day 19</td>
</tr>
</tbody>
</table>
Do cuffed endotracheal tubes increase the risk of airway mucosal injury and post-extubation stridor in children?

Report by

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doi: 10.1136/adc.2005.077651

You are a paediatric registrar on the children's intensive care unit. You are about to intubate a 2 year old child with severe meningococcal septicaemia. Your recent experience in ventilating children with this condition is that they often develop acute respiratory distress syndrome, and require high pressures to maintain adequate oxygenation and ventilation. At these high pressures significant leaks occur around the endotracheal tube, impairing effective ventilation, and on occasion it is necessary to change to an endotracheal tube of greater diameter. Re-intubation under such circumstances carries a greater risk of hypoxia because of the inevitable loss of positive airway pressure during the procedure. You think it would be wise to insert a cuffed endotracheal tube, in which the cuff could be inflated if leak becomes a problem. It has been traditionally taught that only uncuffed endotracheal tubes should be used for intubation in children under the age of 8 years to decrease the risk of airway mucosal injury and post-extubation stridor. You wonder if there is any evidence to the above statement.

Structured clinical question
In children needing intubation [patients], are cuffed endotracheal tubes [intervention] associated with increased incidence of post-extubation stridor/increased risk of airway mucosal injury [outcome]?

Search strategy and outcome
Strategy
Cochrane and PubMed.
Cochrane—endotracheal tube.
Pubmed—cuffed endotracheal tube AND children.
Limits—RCT, English and child <18 years.

Outcome
Cochrane central register of controlled trials—1.
Pubmed—1 RCT (same study as in Cochrane register).
Limits excluding RCT—15 hits, of which 3 were relevant (1 review and 2 case control studies).
See table 4.

Commentary
Traditionally it has been taught that only uncuffed endotracheal tubes (ETT) should be used for children under the age of 8 years. Concerns regarding the use of cuffed ETts originate from studies in adults and animals which indicate that cuffed tubes impair tracheal mucosal blood flow and are associated with higher incidence of post-extubation laryngeal oedema and tracheal stenosis. The pathological process of stenosis is thought to begin with tracheal tube pressure on the laryngotracheal mucosa, especially when the tube is too large or when the cuff is too inflated, causing mechanical oedema and ischaemic necrosis, followed by organisation into fibrotic tissue. However these data described the use of high-pressure, low-volume cuffed ETTs. Studies have documented a causal relation between the duration of intubation and the occurrence of laryngeal mucosal inflammation for cuffed and uncuffed ETTs. Subsequent studies using the modern high-volume, low-pressure cuffs have not shown any increase in the incidence of post-extubation stridor. In fact cuffed ETTs have been shown to decrease the number of laryngoscopies, reduce the risk of aspiration, and improve end-tidal CO2 monitoring. None of the studies were designed to compare incidence of subglottic stenosis between children intubated with cuffed or uncuffed endotracheal tubes. A cases series from France of five children with subglottic stenosis found that only one had immediate post-extubation stridor, with the others developing symptoms of dyspnoea 4–13 days after extubation. For this reason, it cannot be assumed that the absence of immediate

REFERENCES

This case is based on experience from several cases. Details have been altered to ensure patient anonymity.
post-extubation stridor means that subglottic stenosis will not develop. Future studies should be designed with subglottic stenosis as an endpoint before routine use of cuffed endotracheal tubes could be recommended.

CLINICAL BOTTOM LINE

- The use of low-pressure, high-volume cuffed endotracheal tubes is not associated with increased incidence of post-extubation stridor in children. (Grade C)
- There are no studies which adequately assessed potential long term consequences such as subglottic stenosis. (Grade D)
- In selected cases in whom high airway pressures are anticipated during their intensive care stay, cuffed endotracheal tubes can be used to avoid the need for reintubation because of air leak around the ETT. (Grade C)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khine et al (1997)</td>
<td>Children aged from term newborns to 8 y who required tracheal intubation as a part of anaesthetic care. 251 children with odd medical record numbers were assigned to the cuffed tube group, and 237 children with even numbers were assigned to the uncuffed tube group. Children with a history or physical evidence of intrinsic or extrinsic airway obstruction or surgery or those who required nasotracheal intubation were excluded.</td>
<td>RCT (1b)</td>
<td>1. Incidence of croup (post extubation stridor) 2. Number of intubations required to achieve an appropriately sized tube 3. Concentration of nitrous oxide in operating room 4. The need to use more than 21 min sup-1 fresh gas flow</td>
<td>6 (2.4%) patients in the cuffed tube group and 7 (2.9%) patients in the uncuffed tube group had signs or symptoms of group 3 and 3 patients in each group were treated with racemic epinephrine. None of them required reintubation 3.0 (0.1%) patients in the cuffed tube group required a second tube while 54 (22.7%) patients required a second tube in the uncuffed group. Nitrous oxide concentration at 24 inches from patients mouth was greater when uncuffed tracheal tubes were used (p&lt;0.001)</td>
<td>Not blinded. Mallinkrodt lopro or Sheridan low-pressure cuffed endotracheal tubes were used and duration of intubation was 60 minutes</td>
</tr>
<tr>
<td>Deakers et al (1994)</td>
<td>A total of 243 patients had 282 intubations in a paediatric intensive care unit setting. Of the 243 patients, 123 (49%) had cuffed endotracheal tubes. Analysis was performed for 188 (77%) of 243 patients. Patients who died, or had a history of upper airway obstruction or surgery to the upper airway were excluded.</td>
<td>Prospective Case control study (3b)</td>
<td>1. Incidence of post-extubation stridor 2. Frequency of cuffed endotracheal tube use 3. Any increase risk of long-term post extubation complications</td>
<td>Incidence of stridor: (a) cuffed endotracheal tube, 15.1%; (b) uncuffed endotracheal tube, 14.7% [RR 1.02, CI (0.5, 2.34)] 2 patients from the cuffed endotracheal group and 4 from the uncuffed group required reintubation for post extubation stridor. There was no significant difference in rates of stridor when the subgroups under 1 y and aged 1–5 y were compared 33 (17%) of the 188 patients required readmission to the hospital during the next 18 months. None of these had problems with upper airway</td>
<td>Not randomised. Low pressure, high-volume cuffed endotracheal tubes were used</td>
</tr>
<tr>
<td>Newth et al (2004)</td>
<td>597 children &lt;5 years of age, with 210 having cuffed tubes and 387 having uncuffed tubes were included. Setting was a paediatric intensive care unit.</td>
<td>Prospective case control study (3b)</td>
<td>Rate of post-extubation stridor</td>
<td>Racemic epinephrine use in children with uncuffed tube: 6.1% in children &lt;1 month old, 6.7% in children 1–2 years of age, and 9.4% in children 2–5 years of age. Racemic epinephrine use in children with cuffed tube: 7.4% in children &lt;1 month old, 9.5% in children 1–2 years of age, and 8.8% in children 2–5 years of age</td>
<td>Not randomised</td>
</tr>
</tbody>
</table>

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