

Towards evidence based medicine for paediatricians

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In order to give the best care to patients and families, paediatricians need to integrate the highest quality scientific evidence with clinical expertise and the opinions of the family.¹ *Archimedes* seeks to assist practising clinicians by providing “evidence based” answers to common questions which are not at the forefront of research but are at the core of practice. In doing this, we are adapting a format which has been successfully developed by Kevin Macaway-Jones and the group at the *Emergency Medicine Journal*—“BestBets”.

A word of warning. The topic summaries are not systematic reviews, through they are as exhaustive as a practising clinician can produce. They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature. What *Archimedes* offers are practical, best evidence based answers to practical, clinical questions.

The format of *Archimedes* may be familiar. A description of the clinical setting is followed by a structured clinical question. (These aid in focusing the mind, assisting searching,² and gaining answers.³) A brief report of the search used follows—this has been performed in a hierarchical way, to search for the best quality evidence to answer the question.⁴ A table provides a summary of the evidence and key points of the critical appraisal. For further information on critical appraisal, and the measures of effect (such as number needed to treat, NNT) books by Sackett⁵ and Moyer⁶ may help. To pull the information together, a commentary is provided. But to make it all much more accessible, a box provides the clinical bottom lines.

The electronic edition of this journal contains extra information to each of the published *Archimedes* topics. The papers summarised in tables are linked, by an interactive table, to more detailed appraisals of the studies. Updates to previously published topics will be linked to the original article when they are available.

Electronic-only topics that have been published on the BestBets site (www.bestbets.org) and may be of interest to paediatricians include:

- Surgery or indomethacin as the treatment for symptomatic PDA in preterm infants?

Readers wishing to submit their own questions—with best evidence answers—are encouraged to review those already proposed at www.bestbets.org. If your question still hasn't been answered, feel free to submit your summary according to the Instructions for Authors at www.archdischild.com. Three topics are covered in this issue of the journal.

- Should a neonate with possible late onset infection always have a lumbar puncture?
- Does continuous insulin infusion improve glycaemic control and nutrition in hyperglycaemic very low birth weight infants?
- Should premedication be used for semi-urgent or elective intubation in neonates?

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What do you want to do today?

Picking outcomes is extremely important. This month, we have three neonatally focused Archimedes topics. They come up with clinical bottom lines which may surprise, annoy, or bore the reader. Take the subject of lumbar punctures in neonates; performing them—or avoiding them. If you have a strong opinion about this topic it is likely to be drawn from years (well, months) of experience, seeing babies doing generally very well with/without a spinal tap, and deciding that your course of action is likely to be the most beneficial. Malbon *et al* argue that all babies with suspected sepsis should undergo a lumbar puncture “to diagnose meningitis”. What if they had chosen instead to ask instead “to prevent neuropsychological disability”? Or if they had asked whether the undertaking, or avoiding, of spinal taps makes families more or less anxious? Would the clinical bottom line be the same?

Similar suggestions can be made about our other two topics: Does improving weight gain and calorie intake matter over the short time frame of insulin infusions versus calorie restriction, or is the important outcome weight at discharge from the neonatal unit, or neurodisability at 1 year? When it comes to intubation, does data from careful studies, with practitioners primed in the use of anaesthetic agents, translate into everyday life on a neonatal unit?

We all ask specific questions, focusing on specific outcomes. It is interesting to pose slightly different questions to each query we have, to challenge our assumptions and test out different perspectives. For one clinician, diagnosing meningitis may be an important end in itself. To another, the nature of a septic episode may be far less important than the proven outcomes. The process of evidence based practice will never bring these two together, but it may make transparent where the argument should focus.

“Be careful what you wish for, it might come true” may be a warning we take away when asking any clinical question. What do we really want to do today?

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Additional information on each of the topics is available on the ADC website (www.archdischild.com/supplemental)

Should a neonate with possible late onset infection always have a lumbar puncture?

Report by

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A baby born at 28 weeks gestation initially has no respiratory disease and is breathing spontaneously in room air. On day 6 of life the baby develops increasingly frequent and severe apnoeas and episodes of bradycardia that are mostly self-limiting. In view of this, nasal continuous positive airway pressure is started, a blood culture taken, and broad spectrum antibiotics commenced. On the ward round the next morning there is a debate as to whether a lumbar puncture (LP) should also have been performed, as part of the investigations for bacterial infection. The registrar opines that this was considered, but that the baby was thought "too unstable" for the procedure.

If an LP is performed routinely as part of the investigations for infection, how often will it be informative?

Structured clinical question

In neonates [patient] what is the incidence of meningitis [outcome] in late onset infection [greater than 48 hours]?

Search strategy

Secondary sources: Cochrane and Dare: no relevant results.

Primary sources: searched Medline, Pubmed, Embase and CINAHL databases via Dialog Datastar with the search criteria detailed in table 1.

Number of hits: 26, of which five were relevant clinical studies.

Reviews and non-English language papers were excluded.

See table 2.

Commentary

Meningitis is an important complication of late onset neonatal infection. In the five studies cited, CSF culture was positive in 1.3–3.5% of babies with suspected infection. These studies covered the period 1980 to 2004, during which time the incidence of meningitis does not seem to have changed. There appear to be epidemiological differences, with a lower prevalence of late onset meningitis in neonates in the UK.¹

This has implications for treatment, such as the increased length of therapy or the choice of antimicrobial agent, where agents with higher CSF penetration may need to be considered. The mortality and morbidity in late onset meningitis is higher than in early onset meningitis. Blood cultures may often be negative in these babies, causing antibiotics to be discontinued too soon.

The studies are in agreement that 15–30% of babies with meningitis (CSF culture positive) have negative blood cultures.² Some of this may be due to the presence of viral or fungal infections, while others are due to meningitis without bacterial infection. This highlights the importance of routinely performing an LP in the investigation of late onset infection.

Except for the study by Visser and colleagues,³ LPs were not performed routinely for investigation of infection. They were more likely to be performed if the blood cultures were positive, and even then only 60% of such babies had LPs performed. Therefore, it is likely that there is an under-estimation of the prevalence of meningitis. Visser *et al* found that nearly one third of septic babies had coexisting

Table 1 Search criteria

No.	Search term	Results
1.	Neonatal ADJ meningitis	115
2.	MENINGITIS-BACTERIAL#.D.E	4335
3.	INFANT-NEWBORN#	104862
4.	2 AND 3	543
5.	1 OR 4	601
6.	Spinal ADJ puncture	1082
7.	SPINAL-PUNCTURE#.D.E	1043
8.	6 OR 7	1082
9.	5 AND 8	26

meningitis.³ Other studies, except for that of Kumar and colleagues,⁴ have not investigated this proportion, though all studies showed a similar overall incidence of meningitis.

Late onset meningitis is associated with a variety of organisms, though they are predominantly Gram negative. There is a higher incidence of viral and fungal (commonly *Candida albicans*) organisms than in early onset infection. Episodes of group B streptococcal infection can present late and are more likely to be associated with meningitis. All studies excluded diphtheroids and *Staphylococcus epidermidis* as being contaminants, unless they were grown in multiple cultures and there was a clinical indication of infection.

The low rates of LP in the studies are attributed to the perceived adverse effects of the procedures, where babies are considered "too sick to tap". Complications that have been described in the literature include trauma, introduction of infection, spinal epidermoid tumours, brain stem herniation, and hypoxic stress for the baby. In the studies reviewed, none of the above complications were reported.⁴ In the study by Stoll and colleagues there was no difference in the risk of death between infants who did and did not have an LP.⁵ However, meningitis increased the risk of death substantially (23% mortality in babies with meningitis versus 9% in those who had an LP but no meningitis).

The study by Stoll and colleagues⁵ found that among patients who had an LP performed, there was no significant difference across centres in the rate of positive CSF cultures (confirmed in this review). This finding suggests that, although there are LP practice differences across centres, they probably are not explained by better clinical acumen. The study also found that 10 of 90 repeat LPs grew the same organism as the original CSF culture, emphasising the importance of a repeat LP to determine that meningitis has been appropriately treated.

Although the number of babies to investigate for possible bacterial infection in order to diagnose one case of meningitis may seem high, lumbar puncture in this population seems to be safe, the treatment (intravenous antibiotics) is effective, and the event (meningitis) and the implications of missing it are potentially very serious.

CLINICAL BOTTOM LINE

- In neonates with late onset infection the prevalence of meningitis varies from 1.3% to 3.5% (depending on the patient population). (Grade B)
- 30–90 babies (depending on the patient population) who are already being investigated for serious bacterial illness would need to have an LP to detect one baby with meningitis. (Grade A)
- At least 15% of neonates with meningitis may have a negative blood culture. (Grade A)
- Lumbar puncture should be considered as part of the routine investigation of late onset infection (after 48 hours) in neonates. (Grade B)

Table 2 Use of lumbar punctures in neonates with possible late onset infection

Citation, country	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Visser <i>et al</i> (1980), Kansas City, USA ³	400 neonates of whom 193 babies had concurrent blood and CSF cultures for suspected late onset (>72 h) sepsis Gestation: 25–42/40 Birth weight: 634–5650 g	Retrospective cohort (level 2b)	Prevalence of positive CSF culture in the study group	2.5% (5/193) CSF samples positive 10% (21/193) blood cultures positive 24% of septic babies had meningitis (5/21) 15% had concurrently negative blood cultures No reported adverse effects	Meningitis likely to be under diagnosed as retrospective study All babies with suspected sepsis had lumbar punctures performed routinely before antibiotics were started
Schwarsenski <i>et al</i> (1991), Miami, USA ²	826 neonates who underwent an LP, out of which 114 had LPs performed at greater than 1 week of age (late onset) Birth weight: less than 1500 g to greater than 2500 g	Prospective (level 1b)	Prevalence of positive CSF culture in study group	3.5% (4/114) had meningitis. There were 8 positive CSF cultures, but 4 were considered contaminants 25% (1/4) had concurrently negative blood cultures No reported adverse effects	Included LPs done for post haemorrhagic hydrocephalus with raised ICP (8) Under estimation of meningitis as babies >72 h but <1 week, included in early onset
Hristeva <i>et al</i> (1993), Oxford, UK ¹	736 babies underwent an LP, of which 225 had LPs performed late (at >48 h of age) 88 of these were <31 weeks gestation	Prospective (level 1b)	Prevalence of positive CSF culture in study group	1.3% (4/310) cultures were positive Of 88 babies <31 weeks, 6 had late meningitis (4 bacterial; 2 fungal) i.e. 6.8% prevalence (personal correspondence with authors) No mention of number of concurrent negative blood cultures 1 case of probable post-traumatic meningitis reported	High proportion of babies had an LP (42% of all admissions) Babies with respiratory distress had LPs deferred, thereby possibly underestimating the adverse effect
Kumar <i>et al</i> (1995), India ⁴	169 neonates who underwent an LP for suspected sepsis (119 of which were late onset) Gestational: <33–>36/40 Birth weight: <1500 g–>2500 g	Prospective (level 1b)	Prevalence of positive CSF culture in study group	3.3% (4/119) had positive CSF findings 11% had positive blood cultures All babies with meningitis had negative blood cultures No adverse effects of LP reported	Extensive antibiotic use present due to the higher risk population and this may underestimate incidence of meningitis Late onset clearly defined. Appears to be >7 days
Stoll <i>et al</i> (2004), USA ⁵	2877/9641 (30%) had LP>72 h and 6056 (63%) had blood cultures at >72 h Gestation: <25–>33/40 Birth weight: >400–1500 g Average age at LP: 22 days (median: 16 days, range: 4–120 days)	Prospective multi-centre study (level 1b)	Prevalence of positive CSF culture in study group	2.2% (134/6056) had positive CSF cultures 5% (134/2877) of all lumbar punctures were positive (not all septic babies had lumbar punctures) 7.2% of those with positive blood cultures had meningitis 30% (45/134) with meningitis had negative blood cultures Babies with meningitis (compared to those uninfected) were: – ventilated longer (28 v 18 days) – in hospital longer (91 v 79 days) – more likely to fit (25% v 2%) – more likely to die (23% v 2%) There was no difference in the risk of death between infants who did and did not have lumbar punctures [284/2877 (10%) v 661/6764 (10%)]	Study included only very low birth weight babies (<1500 g). This might overestimate risk as the VLBW is the susceptible population 11% of LPs repeated within 10 days were positive for the same organism even though the babies were on treatment with antibiotics

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Does continuous insulin infusion improve glycaemic control and nutrition in hyperglycaemic very low birth weight infants?

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A 1000 g neonate develops persistent hyperglycaemia, glycosuria, and osmotic diuresis on day 2 of total parenteral nutrition. The specialist registrar decides to restrict glucose content in total parenteral nutrition (TPN).

However, the consultant disagrees and decides to start a continuous insulin infusion while administering full TPN to control blood glucose and achieve weight gain. Is the consultant's decision based on sound evidence?

Table 3 Continuous insulin infusion in VLBW infants

Citation, country	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Meetze <i>et al</i> (1998), USA ¹	Extremely low birth weight infants (ELBW) were enrolled on day 2 of life (n=56). Intravenous glucose increased incrementally to a maximum of 12 mg/kg/min. Infants who developed hyperglycaemia were randomly assigned to receive insulin infusion (n=12) or glucose reduction (n=11). Infants whose blood sugars remained normal served as controls (n=33). Hyperglycaemia was defined as single blood sugar >13.3 mmol/l or repeated blood sugars >8.8 mmol/l for at least 4 h	Randomised controlled trial (1b)	Glycaemic control Days to reach 60 kcal/kg/day (non-protein energy)	Euglycaemia (target blood sugar levels not documented) Insulin group: 14/14 infants Glucose reduction group: 9/11 infants Hypoglycaemia episodes (blood glucose <3.3 mmol/l): none in either group Insulin group: 5.5±0.6 days Glucose reduction group: 8.6±1.3 days Control group: 4.1±0.2 days (mean ± SEM) (p<0.01)	Small sample size. Randomisation procedure not explained. Analysis not based on intention to treat (2 infants from glucose reduction group assigned to insulin group). It is not clear why infants in the insulin group had lower intake of calories, protein, and fat than normal controls. Enteral intake was not controlled by the study protocol. Net weight gain between groups not compared.
Collins <i>et al</i> (1991), USA ²	ELBW infants (n=24) with hyperglycaemia were randomly assigned to receive insulin along with total parenteral nutrition (n=12) or standard care (control; n=12) with an aim to achieve 120 kcal/kg/day Glucose intolerance in the control infants was managed by reducing intravenous glucose administration to maintain serum glucose values <9.9 mmol/l without glucosuria Hyperglycaemia was defined as blood glucose >9.9 mmol/l with glycosuria	Prospective randomised controlled trial (1b)	Glycaemic control Calorie intake (non protein energy) Weight gain	Euglycaemia (target blood sugar between 3.9 and 7.7 mmol/l): achieved in both groups Hypoglycaemia episodes (blood glucose <2.2 mmol/l): 4/1848 (0.2%) measurements Insulin group: 124.7±18 Control group: 86.0 ± 6 kcal/kg/day (mean ± SD) (p<0.01) Insulin group: 20.1 ± 12.1 Control group: 7.8±5.1 g/kg/day (mean ± SD) (p<0.01)	Small sample size. Glucose delivery rates used are higher than usual in clinical practice. The incidence of sepsis was significantly greater in control infants (p<0.05)
Binder <i>et al</i> (1989), USA ³	ELBW infants (n=76) with hyperglycaemia were retrospectively reviewed, n=34 received insulin whereas n=42 did not Hyperglycaemia was defined as blood glucose associated with ≥0.5% glycosuria	Case series (4)	Glycaemic control Days to achieve 100 kcal/kg/day Days to regain birth weight	Hypoglycaemia (blood glucose <2.2 mmol/l) 26/7368 (0.5%) measurements Insulin group: 15±8 days Non-insulin group: 17±11 days (mean ± SD) (p=0.21) Insulin group: 12±6 days Non insulin group: 13±6 days (mean ± SD) (p=0.34)	Retrospective case note review. Insulin group had a significantly lower birth weight and gestational age. Despite lower mean birth weight in the insulin group their discharge weight was higher than the control group.
Heron and Bourchier (1988), New Zealand ⁴	Infants <1250 g (n=15) with hyperglycaemia were commenced on insulin infusion	Case series (4)	Glycaemic control Calorie intake	Hypoglycaemia (blood glucose <2 mmol/l): 28/998 (2.8%) measurements Increased post insulin infusion from 60.8±25.1 to 79.9±24.5 kcal/kg/day (mean ± SD) (p<0.001)	Small numbers, uncontrolled study. The upper limit of blood sugar chosen for hypoglycaemia is lower than the standard of 2.2 mmol/l
Ostertag <i>et al</i> (1986), USA ⁵	VLBW infants with hyperglycaemia (n=10) were commenced on insulin	Case series (4)	Glycaemic control Calorie intake Weight gain	Hypoglycaemia (blood glucose ≤1.4 mmol/l): none Post-insulin infusion calorie intake increased from 49.5±32 to 70.4±21 kcal/kg/day (mean ± SEM) (p<0.01) -23±39 increased to +13±34 g/day (mean ± SEM) (p<0.01)	Small numbers, uncontrolled study. The upper limit of blood sugar chosen for hypoglycaemia is lower than the standard of 2.2 mmol/l
Vaucher <i>et al</i> (1982), USA ⁶	VLBW infants with hyperglycaemia (n=10) were commenced on insulin	Case series (4)	Glycaemic control Calorie intake Weight gain	Hypoglycaemia (blood glucose <1.4 mmol/l): <1% of all glucose estimations Post-insulin infusion calorie intake increased from 29 to 56 kcal/kg/day Net weight gain 8/10 infants	Small numbers, uncontrolled study. The upper limit of blood sugar chosen for hypoglycaemia is lower than the standard of 2.2 mmol/l

Structured clinical question

In hyperglycaemic very low birth weight (VLBW) neonates on parenteral nutrition [patient] does addition of insulin therapy without glucose restriction [intervention] improve glycaemic control and weight gain [outcome]?

Search strategy and outcome

Primary search: the Cochrane Library (2005, issue 2). Search term [hyperglycemia AND insulin]. Search results: 560 controlled trials in CENTRAL of which two were relevant and 19 were reviews that were not relevant.

Secondary search: Pubmed and Medline 1966–2005, Embase 1974–2005, Cinahl 1982–2005 using Dialog DataStar. Search term [hyperglycemia AND insulin]. Filter clinical queries. Limit to newborn, human and English language. Search results: Pubmed (17), Medline (19), Embase (75) and Cinahl (1) of which two were controlled trials (already retrieved by Cochrane) and four were case series.

See table 3.

Commentary

Hyperglycaemia occurs commonly in preterm neonates admitted to intensive care, with a reported incidence of 40–80% among VLBW (1000–1500 g) neonates.^{7–9} Hyperglycaemia usually develops when premature infants are given parenteral alimentation in amounts necessary to meet requirements for adequate growth.^{7–8} It can lead to osmotic diuresis with resultant dehydration and electrolyte imbalance.¹⁰ The subsequent hyperosmolar state has been associated with an increased risk of intraventricular haemorrhage.¹¹ The standard approaches to the management of hyperglycaemia in the neonate involve the use of continuous insulin infusion, glucose restriction, or both.¹² It is not clear which of these strategies is more effective in the short term control of hyperglycaemia and optimising nutrition in this vulnerable population. The resting energy expenditure in premature infants is considered to be about 60 kcal/kg/day.¹³ Glucose restriction may cause caloric deprivation and lead to suboptimal postnatal growth, and in VLBW infants may retard head circumference with consequent neurodevelopmental problems.^{14–15} On the other hand continuous insulin infusion may cause hypoglycaemia and hypokalaemia. Moreover, the long term clinical significance of large doses of exogenous insulin in association with early high energy intake in the preterm neonate is unknown.

In adult post-surgical and burns injury patients, uncontrolled hyperglycaemia has been associated with increased episodes of sepsis.^{16–19} Recent studies involving use of insulin for rigid blood glucose control in hyperglycaemic adult intensive care patients have shown significant decrease in their mortality, intensive care stay, and incidence of sepsis.^{20–21} A similar study² in neonates has also shown a reduction in the incidence of sepsis. Studies in patients with post-myocardial infarction have also suggested an improved long term outcome in patients who received insulin and had better glycaemic control.²² It is difficult to delineate the contribution of anabolic effects of insulin to these beneficial effects.

Fetal plasma insulin increases with gestation, largely determined by the glucose flux across the placenta.²³ At birth the disruption of placental supply of nutrients leads to a period of catabolism, and birth weight is not usually recovered until 7–10 days of age. The blood glucose levels during this period are maintained by gluconeogenesis and glycolysis driven by counter regulatory hormones such as catecholamines, growth hormone, and cortisol, diverting glucose utilisation from muscle to brain. The very high blood sugar levels in the first few weeks of life may therefore reflect insulin resistance and/or relative insulin deficiency. The practice of early TPN may also increase the likelihood of hyperglycaemia.²⁴ Administration of intravenous

fat emulsion has been shown to increase plasma glucose concentration by 24% over baseline values.²⁵ An additive effect has been noted when glucose and amino acids were added to the intravenous fat emulsion.²⁶ In contrast the establishment of oral feeds and the coupling of food related nutrient and hormonal signals increase the release of insulin.^{27–29} However, in the VLBW infants it may not be possible to initiate oral feeding and thus induce normal insulin secretion. This leads to prolongation of the catabolic state and as a consequence birth weight may not be regained for several weeks. Fetal growth restriction in animal models has been shown to be associated with impaired pancreatic development and a reduced β -cell mass,^{30–31} which may have long term implications.

Insulin replacement during this catabolic neonatal period may potentially limit proteolysis,³² and improve anabolism and weight gain. Furthermore, improved glycaemic control may help reduce the risk of sepsis and intraventricular haemorrhage.

The literature search yielded six relevant trials of insulin therapy; two controlled trials, and one case series in extremely low birth weight (ELBW, <1000 g) infants, and three case series in VLBW infants (<1500 g).

Two controlled studies^{1–2} compared insulin therapy to reduction in glucose intake. The study by Meetze and colleagues¹ showed improved glycaemic control without hypoglycaemia and significantly shorter duration to reach resting energy expenditure of 60 kcal/kg/day. It remains to be elucidated whether such short term benefits confer any long term advantages. Collins and colleagues² showed improved glycaemic control, increased caloric intake and weight gain, and decreased incidence of sepsis in the insulin group. However, the glucose delivery rates were much higher than common practise.

All uncontrolled studies except that of Binder and colleagues³ reported improved glycaemic control, and increased caloric intake and weight gain on insulin therapy. However, all studies except Meetze and colleagues¹ and Ostertag and colleagues⁵ reported episodes of hypoglycaemia ranging from 0.2% to 2.8% of all observations in the insulin group. The further exploration of both side effects and the population to consider use of insulin infusions is complicated by the marked variation between studies regarding the definition of hyperglycaemia and hypoglycaemia (see table 3).

CLINICAL BOTTOM LINE

- Insulin therapy in the hyperglycaemic ELBW infant improves blood glucose control, caloric intake, and probably weight gain. It is not clear whether this confers any long term advantage. (Grade B)
- Insulin therapy in the hyperglycaemic VLBW infant between 1000 and 1500 g is difficult to evaluate due to lack of good quality studies in this weight category. (Grade C)
- Hypoglycaemia remains an important complication of insulin therapy. (Grade B)

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Should premedication be used for semi-urgent or elective intubation in neonates?

Report by

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A neonate on the intensive care unit requires semi-urgent intubation. As the procedure is being carried out, the medical student notices that the neonate is struggling, prolonging the procedure, and appears to be in distress. The medical student asks why no medication was

given before the neonate was intubated as this is the procedure in adults and children.

Structured clinical question

In neonates undergoing semi-urgent intubation [patients] should premedication [intervention] be used to facilitate easier intubation with less physiological stress [outcome]?

Search strategy and outcome

Medline: 1966 to present.

Embase: 1980 to 2005 week 27.

Cinahl: 1982 to June week 4 2005.

Using the ovid interface.

{exp Infant, newborn or neonat\$.mp.} AND {exp premedication or premed\$.mp. or exp analgesia or analges\$.mp. or exp hypnotics and sedatives or sedat\$.mp. or exp anaesthesia or anaesth\$.mp. or exp. Muscle relaxants, central or muscle relax\$ or exp fentanyl or fentanyl.mp. or exp morphine or morphine.mp. or exp thiopental or thiopental.mp. or exp atropine or atropine.mp. or exp succinylcholine or succinylcholine.mp. or exp pancuronium or pancuronium.mp. or exp halothane or halothane.mp. or exp alfentanil or alfentanil.mp. or suxamethonium.mp. or sevoflurane.mp.} AND {exp endotracheal intubation or endotracheal intubation.mp. or exp intubation or intubat\$.mp.}. Limit to English language and Newborn infant (birth to 1 month).

Medline search found 459 papers, of which 12 were relevant and of a sufficient quality to be included in the paper.

Embase search found a further one paper.

Cinahl found no further papers.

Two further relevant papers were found by searching through the references from the papers found.

All three databases were searched again combining the above search strategy with [AND {exp pain or pain.mp.}]. No further papers were identified.

See table 4.

Commentary

Intubation is a potentially painful and distressing procedure. It is suggested that such physiological distress may increase neonatal morbidity. Premedication for intubation with potent opiates or anaesthetic agents and muscle relaxants is the routine for children and infants. Premedication is not common practice for the intubation of neonates; Whyte *et al* in 1998 revealed that only 14% of the UK's neonatal units had a written policy for premedication for semi-urgent or elective intubation. Only 37% of the neonatal units surveyed routinely used sedation prior to intubation, and those that did used drug doses that varied by factors up to 200.¹⁶ Premedication is more commonly used for term rather than preterm neonates.^{16–18}

Recent research and debate has focused on whether premedication of the neonate for a routine semi-urgent intubation (that is, when intravenous access is available and difficult intubation is not expected) may be safer and a more effective method than awake intubation.

From the available evidence it is clear that awake intubation is associated with a significantly higher intracranial pressure,^{5 8 10–13} higher blood pressure,^{3 7 11} and more variable heart rate^{2 3 5 12} than premedicated intubation. In addition, the increased time taken to intubate^{2–4 6 7} and the greater number of attempts associated with awake intubation^{2 4 6} may compound these factors and lead to increased morbidity. Studies using thiopentone show significantly lower intracranial pressure, significantly more stable heart rate, and lower blood pressure; fewer attempts to intubate are needed and the time taken to intubate is shorter in neonates premedicated with thiopentone than in

Table 4 Premedication for semi-urgent intubation

Citation, country	Study group	Study type (level of evidence)	Outcome	Key results	Study weaknesses
Lemyre <i>et al</i> (2004), Canada ¹	34 infants randomly assigned to receive morphine 0.2 mg/kg IV or placebo (0.9% sodium chloride), for elective intubation	Double blind randomised control trial. (level 1b)	Duration of severe hypoxaemia Duration of hypoxaemia Duration of procedure Max increase in mean blood pressure Number of attempts Number where intubation was achieved at first attempt Number where intubation needed a rescue intubator Bradycardia during procedure	No significant difference No significant difference No significant difference No significant difference No significant difference No significant difference No significant difference No significant difference	Different levels of experience of people performing the intubations (help called). Variations in time of preoxygenation and hand ventilation
Oei <i>et al</i> (2002), Australia ²	20 infants randomised to awake intubation or premedication with morphine 100 µg/kg, atropine 10 µg/kg and suxamethonium 1 mg/kg	Non-blinded randomised control trial (level 1b)	Heart rate Oxygen saturation Total time taken to complete intubation Number of attempts at intubation	Significantly greater drop in awake infants. (68 ± 47 bpm v 29 ± 39 bpm; p=0.017) No significant difference Significantly shorter in premedicated infants (median 60.5 seconds v 595 seconds; p= 0.016) More than twice as many attempts in the awake group (p=0.01)	Lack of blinding. Small sample size. Groups not completely matched. Two infants had to be moved from the awake group to the premedicated group. In 8 of the intubation attempts the awake infants lowest heart rate and oxygen saturation could not be recorded
Bhutada <i>et al</i> (2000), America ³	30 neonates weighing over 2 kg at birth and requiring semi-elective or elective intubation. Randomised into thiopental 6 mg/kg or the equivalent volume of physiological saline	Randomised, placebo controlled trial (level 1b)	Heart rate Heart rate variability Transcutaneous oxygen saturation Mean blood pressure Time taken to intubate	Significant changes (mean (SE) -0.5 [4.4] v 12.0 [3.2] bpm; p<0.03) Significantly less variable in study group (mean (SE) -2.0 v 19 msec; p<0.01) No significant changes Lesser change in mean blood pressure in thiopental group (mean (SE) -2.9 [1.8] v 4.4 [1.1] mmHg; p<0.002) Significantly shorter in the thiopental group (mean (SE) 2.70 [0.37] v 5.08 [1.10] min; p<0.04)	Lack of blinding. Small sample size
Cook-Sather <i>et al</i> (1998), America ⁴	76 infants semi-urgently or electively intubated. Three groups identified; one awake, one given a rapid sequence induction with thiopental (5-7 mg/kg) and muscle relaxant succinylcholine (2 mg/kg) and one group given a modified rapid sequence induction with thiopental and a muscle relaxant of either succinylcholine, vecuronium (0.1-0.2 mg/kg), rocuronium (0.6-1.0 mg/kg), or atracurium (0.4-0.5 mg/kg)	Prospective, non-randomised, control trial (level 1b)	Number of attempts at intubation Time taken to complete intubation Heart rate Oxygen saturation Complications	Significantly more attempts in awake group (8 for awake v 2 for rapid induction v 5 for modified induction where multiple attempts needed; p=0.028) Significantly longer in awake group (median 63 s for awake v 30 s for rapid induction v 36 s for modified induction; p=0.004) No significant difference No significant difference No significant difference	5 infants in the awake group had to be converted to the modified induction group
Millar and Bissonette (1994), Canada ⁵	14 patients aged 1 to 42 days. Randomised into either awake intubation or thiopentone 5 mg/kg and succinylcholine 2 mg/kg	Randomised control study (level 1b)	Heart rate Systolic arterial blood pressure Anterior fontanelle pressure Oxygen saturation Cerebral blood flow velocity Systolic peak flow velocity Mean flow velocity Diastolic peak flow velocity Cerebrovascular resistance	Significantly elevated heart rate in awake group (+33 bpm; p<0.05) No significant differences between the groups Significantly higher in awake group. (12 mmHg v 3 mmHg p<0.05) No significant differences No significant differences No significant differences No significant differences No significant differences No significant differences	Lack of blinding. Small sample size. Patient age range up to 42 days in the article whereas up to 34 days in the abstract. Data from one patient was not included as it was incomplete. Randomisation method is not described

Table 4 Continued

Citation, country	Study group	Study type (level of evidence)	Outcome	Key results	Study weaknesses	
Pokela and Koivisto (1994), Finland ⁶	20 newborn infants requiring elective tracheal intubation. Randomised to receive pethidine 1 mg/kg or alfentanil 20 µg/kg plus suxamethonium 1.5 mg/kg iv over 1 min. All neonates given glycopyrrolate 3–5 mg/kg 5 minutes before the procedure	Randomised controlled trial (level 1b)	Hypoxaemia	Hypoxaemia evident in all neonates in the pethidine group and 7 of 10 patients in the alfentanil group	Lack of blinding. No method of randomisation documented. Small sample size. No quantification of ease of intubation	
			Duration of hypoxaemia	Significantly longer in the pethidine group (4 min v 1.5 min; $p=0.036$)		
			Time taken to intubate	Significantly longer in the pethidine group (120 seconds v 60 seconds; $p=0.012$)		
			Success at first attempt	3/10 intubations successful at first attempt in the pethidine group and 7/10 successful at first attempt in the alfentanil group		
			Change in mean arterial pressure	No significant difference		
			Change in heart rate	No significant difference		
			Change in plasma β-endorphin and serum cortisol	No significant difference		
			Apnoea	Evident in 3 patients in pethidine group		
Khammash <i>et al</i> (1993), Canada ⁷	28 infants randomised to receive atropine (0.02 mg/kg), atropine and succinylcholine (2 mg/kg), atropine and fentanyl (5 µg/kg), or atropine, succinylcholine, and fentanyl before non-urgent nasotracheal intubation	Randomised control trial (level 1b)	Intubation time	Significantly reduced with succinylcholine and/or fentanyl versus atropine alone (22 ± 7 , 25 ± 10 , 27 ± 7 v 50 ± 22 seconds; $p < 0.05$)	Small sample size	
			Mean arterial pressure	Increased by $\geq 20\%$ after intubation in atropine and atropine/succinylcholine groups ($p < 0.05$)		
			Complications	Chest wall rigidity was found in 3 of the infants in the atropine and fentanyl alone group		
Barrington <i>et al</i> (1989), Canada ⁸	20 preterm neonates undergoing semi-elective intubation were randomised to awake and non-paralysed group or awake and paralysed with succinylcholine (2 mg/kg) group. Both received atropine (20 µg/kg)	Randomised control trial (level 1b)	Heart rate	No significant changes	Lack of blinding. Randomisation did not produce well matched groups with respect to the number of infants undergoing a tube change compared to the number undergoing initial intubation, so an additional 5 non-randomised infants undergoing awake intubation were included. Postnatal ages of succinylcholine group were significantly greater	
			Transcutaneous oxygen tension			Significant fall in both groups during intubation. Higher for the awake and paralysed group than for the awake and non-paralysed group (86 ± 46 torr v 55 ± 23 torr $p < 0.05$)
			Blood pressure			Elevated in both groups. No significant difference during intubation between the groups
			Intracranial pressure			Significantly greater rise in awake and non paralysed group than the awake and paralysed group (41.4 ± 23.3 H ₂ O v 36.8 ± 11.6 cm H ₂ O; $p < 0.05$)
Charlton and Greenhough (1988), UK ⁹	45 neonates needing semi-urgent or elective intubation for surgery. Patients were randomised into awake intubation group, N ₂ O and halothane inhalation group, or thiopentone and muscle relaxant (atracurium or pancuronium) group.	Randomised control study (level 1b)	Blood pressure and heart rate	No significant changes in outcome between awake or anaesthetised groups	Lack of blinding. Not randomised or matched for atropine administration. Small sample size. No preterm neonates. Randomisation not detailed.	

Table 4 Continued

Citation, country	Study group	Study type (level of evidence)	Outcome	Key results	Study weaknesses
Stow <i>et al</i> (1988), Canada ¹⁰	24 infants (less than 8 weeks post-natal age) electively intubated either awake or premedicated with sodium thiopentone 5 mg/kg and suxamethonium 2 mg/kg. Both groups were given atropine 0.02 mg/kg IV	Control trial (level 1b)	Anterior fontanelle pressure (AFP) Heart rate Systolic arterial pressure	Lesser increase in the premedicated than the awake groups (30 mmHg v 15 mmHg; $p < 0.05$) No significant changes Decreased significantly in the premedicated infants during anaesthesia (from 92.5 mm Hg to 77.8 mmHg; $p < 0.05$)	Lack of blinding. Small sample size. Randomisation was not described. Groups not matched for post-conceptual age or weight
Friesen <i>et al</i> (1987), America ¹¹	12 preterm neonates randomised into Group 1 (received atropine 0.02 mg/kg IV or Group 2 (received atropine 0.02 mg/kg IV, pancuronium 0.1 mg/kg IV, and 1 of 4 anaesthetics: 0.75% isoflurane, 0.5% halothane, 20 µg/kg fentanyl, or 2 mg/kg ketamine	Randomised control trial (level 1b)	Anterior fontanelle pressure (AFP) Mean blood pressure	Increased significantly in group 1 (from 7.7 to 23.8 cm H ₂ O; $p < 0.05$), it did not change significantly in group 2. The changes in AFP were significantly different between group 1 and group 2 (+197% change v +25% change; $p < 0.05$) Significant increase in systolic blood pressure (average of 20%) in group 1 ($p < 0.05$). Blood pressure did not change significantly in group 2	Small sample size. Lack of blinding
Kelly <i>et al</i> (1984), Canada ¹²	30 neonates requiring semi-urgent or elective intubation, 10 with either no drugs (control), atropine 0.01 mg/kg IV, or atropine 0.01 mg/kg IV and pancuronium 0.1 mg/kg IV	Randomised control trial (level 1b)	Heart rate Transcutaneous oxygen saturation Blood pressure Intracranial pressure	Decrease was significantly greater for control and atropine groups than pancuronium group (52.2 bpm and 36.2 v 7.3; $p < 0.01$) No difference between the groups No reported difference between the groups Significant increase in all groups. Increase was significantly less in the atropine plus pancuronium group than in the other two groups (11.6 cm v 19.8 cm in control group v 24.8 cm in atropine group; $p < 0.05$)	Lack of blinding. Small sample size
Raju <i>et al</i> (1980), America ¹³	Two groups of neonates and infants, one group (n=4) intubated awake second group (n=5) given halothane, nitrous oxide, and D-tubocurare muscle relaxant then intubated	Control study (level 1b)	Intracranial pressure	Significant increase from the baseline in both groups after intubation (increase of 70.65 ± 8.2 cm H ₂ O; $p < 0.001$ for awake and 19.45 ± 5.1 cm H ₂ O; $p < 0.05$ for D-tubocurare). Significantly higher in infants intubated awake than those who received D-tubocurare ($p < 0.001$)	Small number of infants studied. Lack of blinding. Infants not matched for postnatal age or preoperative intracranial pressure. Randomisation method not described. Not all neonates (7 days to 10 months)
Barrington and Byrne (1998), Canada ¹⁴	269 consecutive nasotracheal intubations carried out on infants aged from 30 minutes–192 days. Premedication was given (atropine 20 µg/kg, fentanyl 3–4 µg/kg, and succinylcholine 2 mg/kg) if an IV was in place and if intubation was not an absolute emergency	Cohort study (level 2b)	Premedication used Success rate Incidence of complications and adverse events	Of the 269 intubations performed, premedication was used in 253 cases and not used in 16 cases 253 premedicated intubations, 194 without incident, 28 required 2 attempts, and 9 required a second attempt with smaller tube 4 infants developed chest wall rigidity, resolved with succinylcholine in 3 cases, self limiting in the other	No control group. Large age range

Table 4 Continued

Citation, country	Study group	Study type (level of evidence)	Outcome	Key results	Study weaknesses
Naulaers (1997), Belgium ¹⁵	18 infants (gestational age 32–42 weeks postnatal age 1–150 days) weighing 1390–5000 g all received methohexital 2.6 mg/kg IV	Cohort study (level 2b)	Sedation	All patients adequately sedated within 2 minutes. 11/18 still sedated at 3 minutes and 4/18 at 5 minutes. All patients moving spontaneously by 10 minutes	Small sample size. No control group used. Infants not matched for gestational age, postnatal age, or weight. One patient received three doses of the drug, all others received one. Results were not assessed for significance
		Relaxation	All patients adequately relaxed within 2 minutes. 12/18 still hypotonic at 3 minutes. 1 patient became hypertonic at 5 minutes, this lasted for 1 minute		
		Sleep	12/18 patients were in a deep sleep after 3 minutes, 5/18 patients still asleep after 5 minutes. By 12 minutes all patients were awake		

control neonates.^{3–5 10} Studies using opiates show a significantly lower blood pressure and shorter duration of hypoxia during intubation, and shorter length of time taken to intubate with a potent opiate than in control neonates.^{6 7} They also show that morphine and pethidine are not the drugs of choice.^{1 6} This is likely to be due to their variable pharmacokinetics and pharmacodynamics in neonates.¹⁶ Muscle relaxant studies show a significantly lower intracranial pressure, improved cerebral perfusion pressure, less heart rate variability, and a shorter time needed to intubate in neonates premedicated with a muscle relaxant than in control neonates.^{7 8 12 13} Chest wall rigidity was reported in three of seven neonates given fentanyl without a muscle relaxant in one randomised controlled trial,⁷ and in four neonates in one cohort study, resolving with suxamethonium in three cases and self limiting in the other.¹⁴ No other studies reported this adverse event when an opiate is used with a muscle relaxant.

Current evidence suggests that for routine semi-urgent intubation of neonates, the use of premedication is a more effective technique, with less potentially harmful physiological fluctuations, than traditional awake intubation.

CLINICAL BOTTOM LINE

- Routine premedication for semi-urgent or elective intubation in neonates produces more optimal intubation conditions (fewer attempts and shorter times) and less potentially harmful physiological fluctuations and pain. (Grade B)
- A potent opiate (fentanyl or alfentanil) or thiopentone with a muscle relaxant is the intubating drug combination of choice. (Grade B)
- More clinical trials are required to determine the optimal premedication strategy.

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