

Evidence-based neonatal medicine in Latin America: what can we learn from the International Neonatal Immunotherapy Study and trials of IVIg?

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Although reliable randomized trials are essential to guide policy and avoid unnecessary expenditure on ineffective treatments, very few babies or pregnant women in Latin America, and in the rest of the world, are recruited into multicenter perinatal trials. Three strategies to address this are (i) to establish clinical research networks for perinatal trials, (ii) to provide hospitals with funding to publish the numbers of patients recruited in multicenter perinatal trials as an indicator of performance, and (iii) to engage parents as full partners in, and advocates for, perinatal trials.

It is important to know when a treatment is ineffective

The recent systematic review by Franco et al.¹ of seven randomised trials of intravenous immunoglobulin (IVIg) in treatment of suspected or proven neonatal sepsis in 3,765 infants found no evidence that IVIg reduces mortality. It also found that IVIg produced a clinically unimportant reduction of 1.24 days in length of hospital stay. These results confirmed the sensible advice, offered by the authors of an earlier Cochrane Review,² that there was "insufficient evidence to support the routine administration of IVIg to prevent mortality in infants with suspected or subsequently proved neonatal infection".

Statistically significant evidence from a meta-analysis is not always reliable

Although the previous Cochrane Review of 10 trials in 378 infants showed that IVIg was associated with a statistically significant reduction in mortality (relative risk 0.58; 95% confidence interval 0.38-0.89, $p = 0.01$),² the Cochrane authors prudently recommended that practitioners should wait for the results of the International Neonatal Immunotherapy Study (INIS), a trial which recruited 3,493 infants in 113 neonatal units in nine countries.³ Importantly, 407 infants in INIS were enrolled from neonatal units in Argentina, coordinated by Centro Rosarino de Estudios Perinatales (CREP), under the direction of Dr. E. Abalos. The INIS trial clearly showed that IVIg did not achieve the moderate improvements in death or major disability which it had postulated.³ When INIS was included in the meta-analysis by Franco et al., the earlier apparent reduction² in mortality disappeared.¹

So, 23 years after the first randomised controlled trial of IVIg in newborns was published in 1988,⁴ current evidence indicates that this expensive product has no place in the treatment of neonatal infection. The neonatal community in Latin America and worldwide deserves credit for having resisted the widespread introduction of IVIg until more reliable evidence became available. Globally, this caution

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has prevented millions of dollars of expenditure on an ineffective treatment. It also illustrates why further large randomised trials are needed to guide policy and ensure the cost effective use of limited resources.

Why was the meta-analysis of 378 infants in the Cochrane Review unreliable?

Small trials, like those in the Cochrane Review,² are more likely to be published if they show a positive result. One reason for this "publication bias" is that researchers are less likely to write up small negative trials or submit them for publication.^{5,6} However, publication bias cannot explain why the previous Cochrane Review showed a positive result, because none of the individual trials was statistically significant. The reason for its misleading result may simply be that small trials are more vulnerable to random error. If perinatal trials are to detect moderate effects reliably, they need thousands, not hundreds.⁷ For example, a trial to show, with 90% power, that IVIg reduced mortality in neonatal sepsis from 20 to 15% with a two sided p value of < 0.01 would require a total of about 4,500 infants.⁷

How can we achieve reliable evidence more rapidly in future?

Perinatal clinical trials like the INIS³ are vital in guiding health care for mothers and babies and protecting health budgets from wasteful expenditure. However, despite the pressing need for more and even larger trials, in most countries very few babies or pregnant women – perhaps fewer than 1% – are currently recruited into randomized trials. The INIS took more than 14 years, from initial conception until final publication. The authors concluded that neonatal sepsis remains a global priority and that "there is a need to step up the testing of promising interventions in large international trials".³ How can this be achieved in Latin America?

Establishing neonatal and perinatal clinical trials networks

A key strategy to ensure faster, more comprehensive recruitment to trials is to establish national Clinical Research Networks, as in the United Kingdom.⁸ These networks have provided essential infrastructure for the set up and delivery of high quality clinical trials and other research across a range of specialties by employing central and peripheral coordinating staff. As a result, between 2006 and 2011 the number of patients recruited to clinical trials and other studies in England increased from about 30,000 to over 550,000 per annum.⁸ One of these Clinical Research

Networks is the Medicines for Children Research Network (MCRN), which supports trials in a wide range of pediatric conditions and treatments, including non-pharmaceutical interventions, and which includes a Neonatal Network.^{8,9} The remit of MCRN includes the prioritisation and design of robust, high quality studies identified in collaboration with children, families, clinicians, and research funders.^{8,9} As an illustration of its potential for rapid recruitment, MCRN enrolled about 1,000 children in a clinical trial of a swine flu (H1N1) vaccine within 8 weeks.⁸ Latin American governments, voluntary and philanthropic agencies could consider the establishment of similar networks to work alongside existing perinatal coordinating centres to ensure rapid recruitment of babies and pregnant women into perinatal trials.

Counting the number of patients enrolled in trials each year: a key performance indicator

Another strategy to assist in establishing these networks is to make the number of infants and pregnant women enrolled in multicentre trials each year a key indicator of performance and to provide funding for hospitals to report this, alongside traditional indicators such as rates of hospital infection, and waiting times for emergency departments or elective surgery.¹⁰

Well-informed parents and consumers: potentially powerful advocates for perinatal trials

Many parents respect the need for research and understand that perinatal trials have contributed to substantial advances in the care of newborn babies.^{11,12} Many parents are willing for their baby to participate in two or more studies at the same time.¹³ Some parents express incredulity that getting reliable evidence from trials and putting it into practice can take decades. Giving parents and the public greater access and information about trials^{11,12} may accelerate the process. Parental support for perinatal trials may be enhanced through online peer support and social media¹⁴ and the ability to discuss any questions they have with other parents.

A third strategy is to equip parents, consumers, and clinicians as integral partners in the design, conduct and implementation of perinatal trials. This is an explicit goal of government policy in the United Kingdom, United States, and Australia.^{11,15-17} With strong partnerships based on trust, transparency, and mutual education, greater involvement by parents and consumers in clinical trials research could help develop a lobby of well-informed lay people to press for the resources needed to resolve the many uncertainties which remain in protecting the health of all newborns, in Latin America and globally.^{11,18} This may be a priority for local clinical networks.¹⁹

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Adolescence: the last frontier

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There are three reasons why a child may die from an acute attack of asthma. First, treatment might be unavailable - typical in resource-poor areas, but common also in so-called affluent countries that seem to have erected financial barriers thereby depriving the impoverished of medical care for their children.¹ Secondly, the asthma attack may have come suddenly, and the child has died before medical attention can be summoned. And third, there may have been medical mismanagement of the attack itself. If a child with acute severe asthma is still alive when admitted to a hospital equipped with an intensive care unit, then survival should be virtually

guaranteed; deaths arise when the attack is mismanaged or the severity underestimated. However, it is clear that even with perfect medical management, some asthma deaths are unpreventable.²⁻⁹ Thus, any childhood asthma death should teach us lessons, and these will vary with circumstances.

Lessons may be learned either from detailed examination of individual deaths or by reviewing large data sets, though each has its advantages as well as its problems. Large datasets may suffer from inaccuracies of reporting and a lack of details that might have been useful - in particular, even discrepant details may lead to fruitful lines of further

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