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Continued uncertainty regarding treatment of patent ductus arteriosus in premature infants and the role of clinical trials

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ABSTRACT

Despite several decades of research into treatments for patent ductus arteriosus (PDA), there is continued uncertainty regarding whether, when, and how best to treat PDA and the long-term consequences. There are almost 5000 babies enrolled into clinical trials, but the questions remain largely unanswered. Many of the trials performed over the period were well designed and addressed important clinical questions, but the results are not necessarily directly applicable to the clinical management dilemmas of today since perinatal care has improved over time per se, the patient population is typically more premature, and there have been technological advances in diagnosis. This article examines some of the approaches taken, how trial designs evolved over time, especially in terms of the patient population and outcomes evaluated, and it offers points to consider when planning future research.

1. A lesson from history

A good place to start our critique, by analogy, is the first ever reported multi-arm trial, conducted by James Lind, a Scottish physician. In the eighteenth century, sailors were dying from scurvy; many different treatments were being used to try to treat the disease. Lord Anson, the Admiral of the fleet, reported in 1748 that 380 out of 510 crew on one of his ships died of the disease. According to Lind, scurvy caused more deaths in the British fleets than French and Spanish arms [1]. Lind quickly realised that "No physician conversant with this disease at sea had undertaken to throw light upon the subject." So, in May 1747, he conducted a trial on 12 patients with the scurvy, on board the Salisbury at Sea. Their cases were clearly described – they all had putrid gums, the spots and lassitude, with weakness of their knees (patients: P). They were housed together in one place (setting), in a proper apartment for the sick in the fore-hold, and they had a common diet. Six different interventions (I) were given to two patients respectively. These ranged from oranges and lemons to sea-water and other concoctions of varying acidity. The results appeared conclusive: one of the men who had taken oranges and lemons was fit for duty after six days, the other also making progress.

1.1. What were the strengths and weaknesses of this trial?

The strengths include the description of and homogeneity of the patient population, the control of diet and movements, and the use of an objective substantive outcome (good for the captain at least). The weaknesses include the tiny sample size, the undocumented process of randomisation, the generalisability of the findings and potential selection bias; two patients with the most severe symptoms were reported to have received sea-water.

1.2. What can we learn from this trial?

Good design and conduct is essential; clarity of definitions, the standardisation of approach, and the use of objective outcomes all help to 'hear a signal above the noise', plus sometimes you get lucky.

2. Review of the 'PDA trials' literature

2.1. Using an example of a trial published in 1983 studying the effects of indomethacin in premature infants with PDA

The design ethos was particularly impressive in terms of deliverability – the trial was designed to "simulate the therapeutic options

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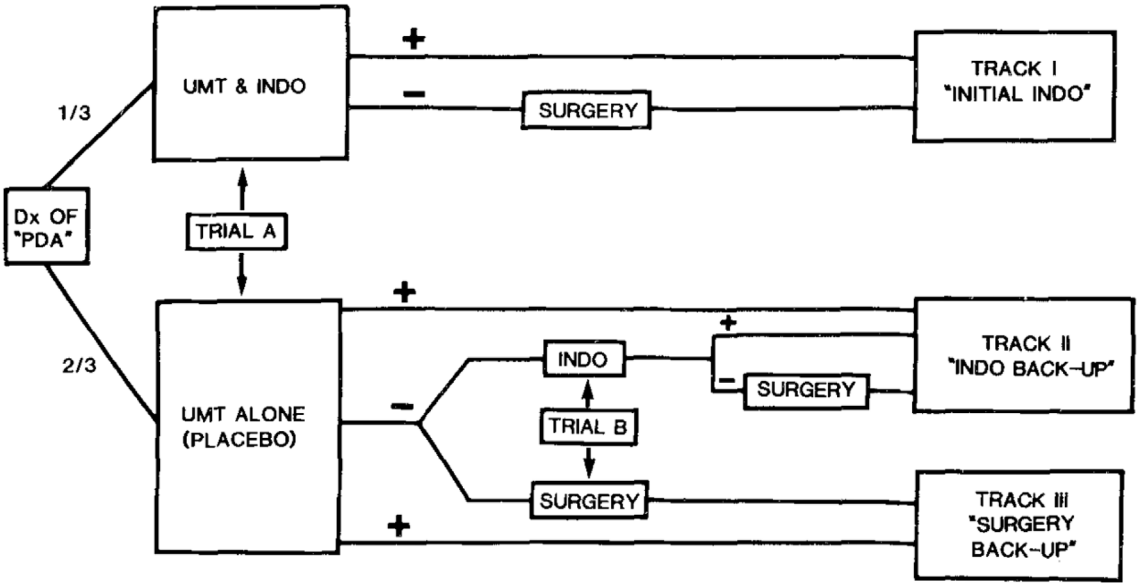

Fig. 1. Schema of study design, summarising randomisation allocations on diagnosis of haemodynamically significant patent ductus arteriosus (PDA) in Trial A and subsequent randomisation in Trial B of infants initially receiving placebo who required back-up therapy. Reprinted from Gersony et al. [2], with permission.

available to clinicians caring for a preterm infant who develops a serious, potentially life-threatening PDA"; a care pathway trial in modern parlance [2]. The participants (P) were 421 new-born infants with birth weight < 1750 g who had developed a haemodynamically significant PDA. One of three regimens (I) could be pursued (Fig. 1):

- *Care pathway 1.* Attempt to reduce the effects of volume overload on the cardiovascular system using an intensive course of 'usual medical therapy' (UMT; e.g. fluid restriction, diuretics, and perhaps digoxin) and at the same time administer indomethacin (UMT + Indo).
- *Care pathway 2.* Perform UMT as described above, but if this approach is not effective within a short period of time (initial re-evaluation at 36–48 h) in ameliorating the clinical impact of the PDA, administer indomethacin.
- *Care pathway 3.* Perform UMT as described above, but if this approach is not effective within a short period of time in ameliorating the clinical impact of the PDA, refer the infant for surgical ligation of the ductus arteriosus.

The primary outcome (O) was ductal closure rate – now considered a surrogate outcome but clearly relevant since the drug is being given with the aim of closing the duct. Secondary outcomes included hospital mortality, incidence of adverse conditions during hospitalisation, length of hospital stay and duration of respiratory support.

This was an elegant but complex design using a two-stage randomisation which addressed two important research questions.

(i) Initial treatment (Trial A) allowed comparison of 'early treatment' (up to 48 h) in indomethacin vs placebo in a targeted high-risk group.
(ii) Trial B allowed a comparison of indomethacin versus surgery in those infants for whom the PDA had not closed by itself within 36–48 h, a 'later treatment' clinical question.

The main comparative analysis was performed on an intention-to-treat basis (ITT), i.e. infants were analysed in their randomised groups irrespective of treatment received. After 48 h of treatment the PDA closure rate was 79% in the indomethacin group versus 28% in the placebo group. This control group event rate rose to 35% without the need for back-up therapy, and this comparison was reported as the primary outcome (closure rate ratio: 2.3; $P < 0.001$). Another finding was that closure rate was related to gestational age.

2.1.1. *What were the strengths and weaknesses of this trial?*

Strengths include the elegance of the design, the clarity of reporting, the trial addressed important (multiple) clinical questions including safety, was embedded in routine clinical practice, and used a multidisciplinary team. It was perhaps ahead of its time, and such a design would be most welcome today. Weaknesses include the complexity (could also be seen as a strength), a lack of a sample size/power calculation, the analysis and interpretation (hypothesis tests did not always compare like with like and the equivalence conclusion regarding the timing of administration of indomethacin is questionable) and multiple subgroup analysis was given too much prominence.

2.1.2. *What can we learn from this trial?*

The bottom line is that embedding a trial within all present treatment options in care pathways will maximise the chances of success by ensuring maximum clinician buy-in. Addressing more than one research question makes the trial not only important but cost-effective.

2.2. *Using an example of a trial published in 1994 studying low-dose indomethacin and prevention of intraventricular haemorrhage*

The aim was to test the hypothesis that low-dose indomethacin would lower the incidence and severity of intraventricular haemorrhage (IVH) [3]. The participants (P) were 431 neonates of birth weight 600–1250 g with no evidence for IVH at 6–11 h of age. The intervention (I) was low-dose indomethacin (0.1 mg/kg intravenously at 6–12 postnatal hours and every 24 h for two more doses) or (comparator C) an equal volume of saline placebo by slow intravenous infusion during a 5–10 min period.

The primary outcome (O) was not explicitly stated but the sample size was based on 'IVH rate', clearly a more substantive outcome than PDA closure and with potential life-long consequences. Secondary short-term outcomes included PDA closure, haemorrhage, bronchopulmonary dysplasia (BPD), mortality, and adverse reactions.

2.2.1. *What were the strengths and weaknesses of this trial?*

Strengths include a sample size/power re-calculation during the trial due to a lower than expected control group event rate;