Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial

SafeBoosC investigators

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thebmj.com

- Research: Non-invasive versus invasive respiratory support in preterm infants at birth (*BMJ* 2013;347:f5980)
- Research News: Encouraging outcomes for Sweden's extremely preterm babies (*BMJ* 2013;346:f2799)
- Research: Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies) (*BMJ* 2012;345:e7976)
- Clinical Review: The extremely premature neonate: anticipating and managing care (*BMJ* 2009;338:b2325)

STUDY QUESTION

Is it possible to stabilise the cerebral oxygenation of extremely preterm infants by the combination of cerebral near infrared spectroscopy (NIRS) oximetry and a dedicated treatment guideline?

SUMMARY ANSWER

The duration and magnitude of cerebral oxygenation outside the target range was reduced by 58%.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The early unstable respiratory and circulatory systems of extremely preterm infants are contributing factors to the development of brain injury in this population. The present study shows that it is possible to stabilise the cerebral oxygenation through the combination of cerebral NIRS oximetry and a dedicated treatment guideline.

Design

A randomised controlled trial with block randomisation and computer generated allocation. We compared visible cerebral NIRS oximetry combined with a dedicated treatment guideline with blinded cerebral NIRS oximetry and standard care during the first three days of life.

Participants and setting

166 infants born before 28 weeks of gestation in eight tertiary neonatal intensive care units in eight European countries.

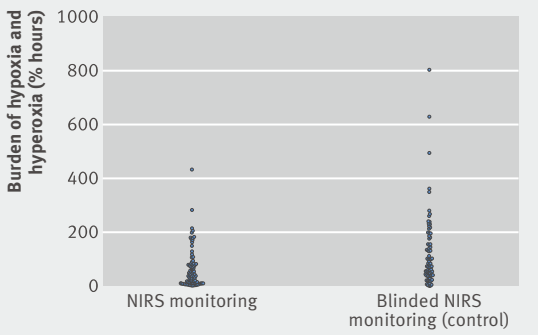
Primary outcome

The primary outcome measure was the time spent outside the target range of 55% to 85% for cerebral oxygenation multiplied by the mean absolute deviation, expressed in %hours (the burden of hypoxia and hyperoxia) during the first three days of life.

Main results and the role of chance

The 86 infants randomised to the NIRS group had a median burden of hypoxia and hyperoxia of 36.1%hours (interquartile range 9.2-79.5%hours) compared with 81.3%hours (38.5-181.3) in the control group, a reduction of 58% (95% confidence interval 35% to 73%, P<0.001). In the experimental group the median burden of hypoxia was 16.6 (interquartile range 5.4-68.1), compared with 53.6 (17.4-171.3) in the control group (P=0.0012). The median burden of hyperoxia was similar between the groups (P=0.98). We found no statistically significant differences between the two groups at term corrected age.

Burden of hypoxia and hyperoxia by treatment group



Harms

No severe adverse reactions were associated with the device. However, 16 infants had marks on the skin from the NIRS sensors: four in the intervention group and 12 in the control group (P=0.03).

Bias, confounding, and other reasons for caution

Out of range cerebral oxygenation (regional tissue haemoglobin oxygen saturation, $rStO_2$) values will on average tend to normalise after repositioning of the sensor (regression towards the mean). This means that any repositioning motivated by out of range $rStO_2$ values will introduce a bias on the primary outcome, reducing out of range $rStO_2$ only in the group with visible NIRS. The treatment guideline is a list of possible interventions, with choice left to the discretion of the attending clinical staff. It was not possible to blind clinical staff to group allocation. This could lead to selective collateral intervention in one of the treatment groups, leading to biased intervention effects. We reduced the impact of this problem by centralised outcome assessments blinded to intervention group.

Generalisability to other populations

It is uncertain if the results can be generalised, as extremely preterm infants pose haemodynamic challenges during the transition after birth, and these may be less important in other populations.

Study funding/potential competing interests

This work was supported by an unconditional and unrestricted grant from the Danish Council for Strategic Research (DKK 11,100,105). All researchers are independent of the funding body. We have no competing interests.

Trial registration number

ClinicalTrial.gov NCT01590316.

Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies

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EDITORIAL by Satija and colleagues

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- Research News: Excess weight causes nearly 4% of new cancers a year worldwide (*BMJ* 2014;349:g7240)
- Research: The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes (*BMJ* 2012;344:e3645)

STUDY QUESTION

What is the strength of the evidence and the extent of potential bias in the claimed literature associations of type 2 diabetes and risk of cancer?

SUMMARY ANSWER

Evidence could be substantiated only for the associations between type 2 diabetes and risk of breast, intrahepatic cholangiocarcinoma, colorectal, and endometrial cancer

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Many studies have examined the association between type 2 diabetes and risk of developing cancer and cancer mortality and strong claims of significance exist for most of the studied associations. This umbrella review of available meta-analyses showed that only a minority of these associations have robust supporting evidence without hints of bias.

Random effects estimates with 95% confidence and prediction intervals from 27 meta-analyses of type 2 diabetes and cancer incidence or mortality

Selection criteria for studies

We conducted an umbrella review of meta-analyses of observational studies in humans that examined the association between type 2 diabetes and risk of developing cancer or cancer mortality. These meta-analyses were identified through searches in PubMed, Embase and the Cochrane database of systematic reviews from inception to the end of 2013.

Primary outcomes

We focused on cancer incidence and mortality but not prognosis after cancer development.

Main results and role of chance

Eligible meta-analyses assessed associations of type 2 diabetes with risk of cancer incidence for 20 cancer sites and cancer mortality for seven cancer sites. The summary random effects estimates were significant at P≤0.05 in 20 meta-analyses (74%), and all reported increased risks of cancer when they compared participants with and without diabetes. Of the 27 meta-analyses, eventually only seven (26%) compiled evidence on more than 1000 cases, had significant summary associations at P≤0.001 for both random and fixed effects calculations, and had neither evidence of small study effects nor evidence for excess significance. Of those, only six (22%) meta-analyses did not also have substantial heterogeneity (I^2>75%) for the associations between type 2 diabetes and risk of breast, cholangiocarcinoma (both intrahepatic and extrahepatic), colorectal, endometrial, and gallbladder cancer. The 95% prediction intervals excluded the null value for four of these associations (breast, intrahepatic cholangiocarcinoma, colorectal, and endometrial cancer).

Bias, confounding, and other reasons for caution

Other associations could be genuine, but there is still substantial uncertainty about them. Future prospective studies and large consortiums with better assessment of type 2 diabetes and its time varying treatment, control, and sequelae and comprehensive standardised reporting of analyses are needed to draw firmer conclusions.

Study funding/potential competing interests

This work was supported by the seventh framework programme of the European Union (PIEF-GA-2010-276017 to KKT and JPAI).

Comparison of two dose and three dose human papillomavirus vaccine schedules: cost effectiveness analysis based on transmission model

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EDITORIAL by Brotherton

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- Editorial: HPV vaccination (*BMJ* 2014;349:g4783)
- Research: Comparing bivalent and quadrivalent human papillomavirus vaccines (*BMJ* 2011;343:d5775)
- Research: Cost effectiveness analysis of including boys in a human papillomavirus vaccination programme in the United States (*BMJ* 2009;339:b3884)

STUDY QUESTION

What is the incremental cost effectiveness of giving three doses of human papillomavirus vaccination to girls under 15 years old, compared with two doses?

SUMMARY ANSWER

Two dose human papillomavirus vaccine schedules are likely to be the most cost effective option provided protection lasts at least 20 years.

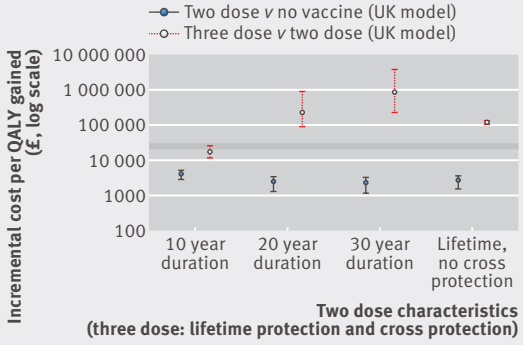
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Two dose human papillomavirus vaccine schedules may provide long-lasting protection against human papillomavirus 16 and 18, but the exact duration and breadth of two dose protection is uncertain. If two doses of bivalent or quadrivalent human papillomavirus vaccines give only 10 years' protection but adding a third dose extends this to lifetime protection, then the third dose also seems likely to be cost effective.

Main results

With a discount rate of 3.5% per annum, giving at least two doses of human papillomavirus vaccine seems to be highly cost effective across the entire range of scenarios considered at the list price for quadrivalent vaccine of £86.50 (€109.23; $136.00) per dose. If two doses give only 10 years' protection but adding a third dose extends this to lifetime protection, then the third dose also seems to be cost effective at £86.50 per dose (median incremental cost effectiveness ratio £17 000, interquartile range £11 700-£25 800). If two doses protect for more than 20 years, then the third dose will have to be priced substantially lower (median threshold price £31, £28-£35) to be cost effective.

Incremental cost per quality adjusted life year (QALY) gained for two dose quadrivalent vaccination (compared with no vaccination) and three dose quadrivalent vaccination (compared with two dose vaccination)



Results are medians and interquartile ranges of 1000 Latin hypercube samples
One vaccine dose was assumed to cost £86.50 for procurement and £9.33 for administration. Discount rate is 3.5%. Shaded area is £20 000-£30 000 per QALY gained

Design

This was a cost effectiveness study based on a transmission dynamic model of human papillomavirus vaccination.

Source(s) of effectiveness

We used data from vaccine trials and from studies after introduction of vaccine showing that short term immune response and efficacy against persistent human papillomavirus 16/18 infection are non-inferior in 9-14 year old girls receiving two doses compared with 15-25 year old female patients receiving three doses.

Data sources

Cost data came from previous economic evaluations of human papillomavirus vaccination in the United Kingdom. The time horizon was 100 years.

Results of sensitivity analysis

Results were similar for a bivalent vaccine priced at £80.50 per dose, with a discount rate of 1.5% per annum, and when we explored the same scenarios by parameterising a Canadian model (HPV-ADVISE) with economic data from the United Kingdom.

Limitations

Results should not be generalised to resource poor settings owing to differences in sexual behaviour, epidemiology of human papillomavirus, coverage of cervical screening, and healthcare costs. We assumed screening to be cytology based; any change to human papillomavirus DNA testing as the primary test is likely to make two dose schedules even more attractive as there will probably be even less disease for the third dose to prevent.

Study funding/potential competing interests

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