An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial

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STUDY QUESTION

Can an early rehabilitation intervention started at the time of admission to hospital for an exacerbation of chronic respiratory disease reduce the readmission rate over 12 months?

SUMMARY ANSWER

An early rehabilitation intervention did not reduce readmission rate in the year after the intervention. Mortality at 12 months was higher in the intervention group.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Admissions to hospital for exacerbations of chronic respiratory disease are associated with high readmission rates. Beyond current standard physiotherapy practice, progressive exercise rehabilitation should not be started during the early stages of the acute illness as it does not reduce the risk of readmission and moreover might cause harm.

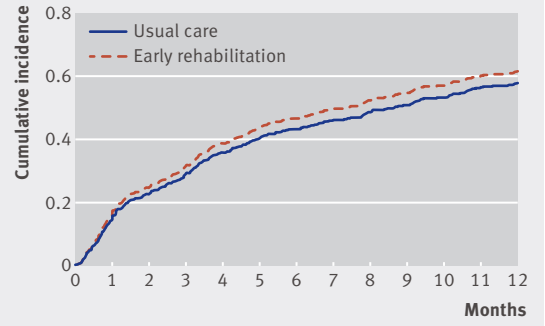
Design

Patients were randomised to early rehabilitation or usual care. Early rehabilitation comprised daily aerobic, strength, and neuromuscular electrical stimulation starting within 48 hours of admission to hospital. The intervention lasted six weeks, with daily supervised training during the inpatient stay and unsupervised training supported with phone calls and a self management programme as an outpatient. Participants were followed up for one year.

Participants and setting

389 patients admitted to hospital with an exacerbation of chronic respiratory disease were recruited. 320 (82%) had chronic obstructive pulmonary disease.

Cumulative incidence of hospital readmission, using competing risks regression analysis



Primary outcome

Rate of admission to hospital at one year.

Main results and the role of chance

233 (60%) participants were readmitted at least once in the following year: usual care 111/193 (58%), early rehabilitation 122/196 (62%). By intention to treat we found no significant difference in the rate of hospital admission at 12 months (hazard ratio 1.1, 95% confidence interval 0.86 to 1.43, P=0.4). Clinically and statistically significant improvements in physical performance were seen in both groups during follow-up. However, there was no difference between the groups apart from the endurance shuttle walk at six weeks, which was in favour of early rehabilitation. The statistical power of the study was sufficient to detect a 15% reduction in readmissions in the intervention group. Given that readmissions were numerically higher in the early rehabilitation group, a type II error is unlikely.

Harms

80/389 (20%) patients died during the trial. Mortality was higher in the intervention group: deaths at 12 months: 49 (25%) early rehabilitation *v* 31 (16%) usual care (odds ratio 1.74, 95% confidence interval 1.05 to 2.88, P=0.03). The mortality observation was unexpected and we cannot exclude the possibility that this occurred by chance.

Bias, confounding, and other reasons for caution

The short duration of inpatient treatment and the frailty of the study population limited the number and intensity of supervised exercise sessions that could be delivered as part of the intervention. The negative outcome may therefore have been explained by insufficient intensity of intervention, although this does not explain the increased mortality in the intervention group. Both groups received physiotherapy on the ward in line with standard UK practice, which may have been sufficient alone to promote reablement, and therefore diminished the added value of the early rehabilitation intervention.

Generalisability to other populations

We recruited participants with a wide range of chronic respiratory diseases, although most had chronic obstructive pulmonary disease. The study population was more frail and disabled than those with stable disease referred for pulmonary rehabilitation but would be representative of patients with chronic obstructive pulmonary disease who are offered outpatient pulmonary rehabilitation after discharge.

Trial registration number

Current Controlled Trials ISRCTN05557928.

Whooping cough in school age children presenting with persistent cough in UK primary care after introduction of the preschool pertussis booster vaccination: prospective cohort study

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STUDY QUESTION

Is pertussis still an important cause of persistent cough among UK school age children since the introduction of the preschool pertussis booster vaccination?

SUMMARY ANSWER

Pertussis can still be found in about a fifth of school age children who present with persistent cough in UK primary care and can cause clinically significant cough, even in fully vaccinated children.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Although the main aim of pertussis vaccination is to reduce the risk of severe pertussis during infancy, an additional adolescent booster may be worth while if the prevalence of pertussis in school age children is sufficiently high to make a national vaccination programme cost effective. Despite high coverage with the preschool booster vaccination, pertussis is still a common cause of persistent cough among school age children in the UK whose cough is sufficiently severe to precipitate a visit to a general practitioner.

Participants and setting

Children aged 5 to 15 years who presented in primary care with a persistent cough of two to eight weeks' duration were recruited from 22 general practices in Thames Valley, United Kingdom.

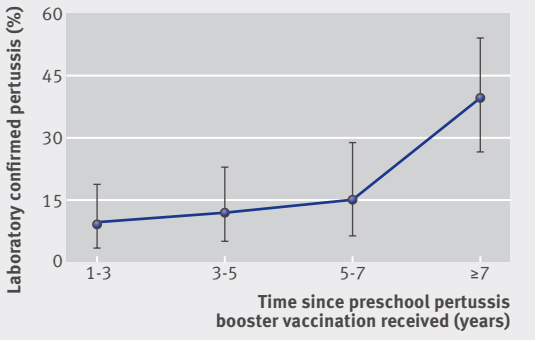
Design, size, and duration

This prospective cohort study recruited 279 participants between November 2010 and December 2012. An oral fluid sample was obtained from each participant and sent to the Health Protection Agency (now Public Health England) for analysis. We analysed samples by using an IgG antigen-capture enzyme-linked immunosorbent assay to detect antipertussis toxin IgG. Laboratory confirmed pertussis was diagnosed in participants with an anti-pertussis toxin IgG titre of at least 70 arbitrary units (aU) in oral fluid. We measured 24 hour cough frequency with the Leicester Cough Monitor in a convenience sample of six fully vaccinated children with laboratory confirmed pertussis.

Main results and the role of chance

Fifty six (20%, 95% confidence interval 16% to 25%) children had evidence of recent pertussis infection, including 39 (18%, 13% to 24%) of 215 children who had been fully vaccinated. The figure shows that the risk of pertussis was more than three times higher (21/53; 40%, 26% to 54%) in children who had received the preschool pertussis booster vaccination seven or more years before than in those who had received it less than seven years before (20/171; 12%, 7% to 17%). Four of six children in whom cough frequency was measured coughed more than 400 times in 24 hours.

Laboratory confirmed pertussis in children presenting in primary care with persistent cough after receiving preschool pertussis booster vaccination (n=224)



Bias, confounding, and other reasons for caution

Our recruitment partially overlapped with a national pertussis epidemic (April 2012 to December 2012). We were unable to record the total number of children who met study eligibility criteria but were not invited to participate in our study. The observed increase in risk of pertussis with time since receiving the preschool pertussis booster vaccination could reflect confounding (for example, changes in age related exposure and herd immunity).

Generalisability to other populations

Temporal variations in pertussis positivity rates in our cohort mirrored those observed in England and Wales during the same period. Recruiting practices covered populations with a broad spectrum of socioeconomic deprivation.

Study funding/potential competing interests

This paper presents independent research funded by the National Institute for Health Research (NIHR) School for Primary Care Research. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. The cough monitor work was funded by an Oxfordshire Health Services Research Committee grant. KW held an NIHR doctoral research fellowship. AH is chairman of the Joint Committee on Vaccination and Immunisation adolescent sub-committee. HC and GA are members of the Public Health England Immunisation Department, which has provided vaccine manufacturers with post-marketing surveillance reports.

Safety of pertussis vaccination in pregnant women in UK: observational study

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STUDY QUESTION

Is the use of a vaccine containing pertussis associated with any adverse events related to pregnancy when administered in the third trimester?

SUMMARY ANSWER

There was no evidence of an increased risk of stillbirth or any of a range of predefined adverse events related to pregnancy after vaccination with a vaccine containing pertussis.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A sharp increase in confirmed cases of pertussis observed in the UK during 2011-12 led to the introduction of a pertussis vaccination programme with Repevax and targeting pregnant women in their third trimester aimed at reducing infant morbidity and mortality. As with most vaccines, use in pregnancy had not been evaluated during clinical development and there were only limited post-marketing data. The study was designed to provide the first controlled data on the safety profile of vaccines containing pertussis in pregnancy and found no evidence of an increased risk of adverse events.

Participants and setting

Pregnant women with a recorded vaccination were identified in the UK Clinical Practice Research Datalink (CPRD), a large database of anonymised general practice electronic medical records. They were compared with both national data from the England and Wales Office for National Statistics and a matched historical unvaccinated cohort also identified in the CPRD.

Design, size, and duration

This observational cohort study was conducted six months after the new recommendation with data to end March 2013. Over 20 000 pregnant women with a record of vaccination containing pertussis were identified. Data extracted included pregnancy outcome, gestational age, birth weight, and instances of maternal or neonatal death, pre-eclampsia/eclampsia, haemorrhage, fetal distress, uterine rupture, placenta or vasa praevia, caesarean delivery, and child renal failure.

Main results and the role of chance

There was no evidence of an increased risk of stillbirth in the 14 days immediately after vaccination (incidence rate ratio 0.69, 95% confidence interval 0.23 to 1.62) or later in pregnancy compared with historical national stillbirth rates (0.85, 0.44 to 1.61). Compared with a matched historical unvaccinated cohort, there was no evidence that vaccination accelerated time to delivery (hazard ratio 1.00, 95% confidence interval 0.97 to 1.02). There was no difference in birth weight. The table presents further results from the comparative matched cohort study. There were no recorded instances of maternal death, antepartum haemorrhage, uterine rupture, placenta abruption, vasa praevia, fetal distress, or child renal failure after vaccination.

Bias, confounding, and other reasons for caution

Given the high uptake of the vaccine we could quickly identify a large number of vaccinated pregnant women with rapid data on outcomes. The study, however, cannot rule out small increases in risks, and we continue to monitor safety. There is the potential for unmeasured confounding and, though women were matched on maternal and gestational age, full adjustment for potential confounders was not conducted. A sensitivity analysis including all women with a pregnancy outcome during the campaign, regardless of vaccination status found no significant increases in the risk of any of the predefined adverse events related to pregnancy after the introduction of the vaccination campaign compared with before. Also, while the GP record should be complete there is a possibility of missing outcome data.

Generalisability to other populations

This study can be used as initial evidence for evaluating the safety of vaccines containing pertussis in pregnancy.

Study funding/potential competing interests

All authors were employed by the Medicines and Healthcare products Regulatory Agency (MHRA), which is an Executive Agency of the UK Department of Health. The MHRA has statutory responsibility to monitor the safety of medicinal products, including vaccines, on the UK market and the study was undertaken independently of the Department of Health.

Overall risk of potential adverse events in women vaccinated against pertussis during pregnancy versus historical unvaccinated controls

Event	No (%) of events		Conditional relative risk (95% CI)
	Vaccinated women (n=6185)	Matched unvaccinated women (n=18 523)	
Stillbirth	12 (0.19)	42 (0.23)	0.85 (0.45 to 1.61)
Neonatal death (within 7 days)	2 (0.03)	6 (0.03)	1.00 (0.20 to 4.95)
Pre-eclampsia/eclampsia	22 (0.36)	54 (0.29)	1.22 (0.74 to 2.01)
Placenta praevia	2 (0.03)	15 (0.08)	0.40 (0.09 to 1.75)
Intrauterine growth retardation/low birth weight/weight <2500 g	126 (2.04)	311 (1.68)	1.20 (0.98 to 1.48)
Caesarean section	1238 (20.02)	3748 (20.22)	0.99 (0.93 to 1.06)
Premature labour (without delivery)	5 (0.08)	21 (0.11)	0.71 (0.27 to 1.89)
Postpartum haemorrhage	59 (0.95)	181 (0.98)	0.98 (0.73 to 1.31)

Familial risk of cerebral palsy: population based cohort study

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EDITORIAL by Rosenboom

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STUDY QUESTION

What are the risks of recurrence of cerebral palsy in family members with various degrees of relatedness?

SUMMARY ANSWER

People born into families in which someone already has cerebral palsy are themselves at elevated risk, depending on their degree of relatedness; elevated r isk may extend even to third degree relatives (first cousins).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Cerebral palsy is most often caused by in utero brain injury, but what inflicts the damage is usually not known. Cerebral palsy seems to include a genetic component, suggesting that the underlying causes extend beyond the clinical management of delivery.

Participants and setting

The participants were 2 036 741 people registered in the Medical Birth Registry of Norway during 1967-2002. We linked data from the birth registry to the Norwegian social insurance scheme to identify 3649 cases of cerebral palsy and to databases of Statistics Norway to identify relatives.

Design, size, and duration

In the study cohort, we identified 22 558 pairs of twins, 1.85 million pairs of first degree relatives, 1.70 million pairs of second degree relatives, and 5.17 million pairs of third degree relatives. We considered cerebral palsy status of the older relative to be the "exposure" and cerebral palsy status of the younger relative to be the "outcome." We estimated relative risks of recurrence as the absolute risk of cerebral palsy in cohort members at risk (younger sibling, offspring, niece/nephew, or younger first cousin of affected people) divided by the absolute risk of cerebral palsy in the reference population (younger sibling, offspring, niece/nephew, or younger first cousin of unaffected people).

Main results and the role of chance

The prevalence of cerebral palsy was 1.8 per 1000 for children born during 1967-2002, higher in twins (5.1 per 1000) than in singletons (1.7 per 1000). If one twin had cerebral palsy, the relative recurrence risk was 15.6 (95% confidence interval 9.8 to 25) for the other twin. In families with an affected singleton child, risk was 9.2 (6.4 to13.1)-fold higher in a subsequent full sibling and 3.0 (1.1 to 8.6)-fold higher in a half sibling, compared with an unaffected singleton. Affected parents were also at increased risk of having an affected child (6.5 (1.6 to 26)-fold higher than unaffected parents). For people with an affected first cousin, we found only weak evidence for increased risk (1.5 (0.9 to 2.7)-fold higher than unaffected first cousin). After exclusion of preterm births (an important risk factor of cerebral palsy), familial risks remained and were often stronger. For instance, for term born children with a first cousin with cerebral palsy the relative recurrence risk was 2.5 (1.1 to 5.7).

Bias, confounding, and other reasons for caution

Use of population based registries and validated data minimise the chance of systematic bias. Confounding by unmeasured variables can never be ruled out. Lack of data on cerebral palsy subtype is a major limitation. Our inferences regarding genetics may be biased by the fact that a person with cerebral palsy has less chance of becoming a parent or a sibling.

Generalisability to other populations

Results may not be generalisable to genetically different populations.

Study funding/potential competing interests

The study has been supported by grants from the University of Bergen and the Western Norway Regional Health Authority and by the Intramural Research Program of the National Institute of Environmental Health Sciences, National Institutes of Health.

Recurrence of cerebral palsy (CP) among relatives. Singletons and twins born in Norway 1967-2002 surviving first three years of life

Unexposed		Exposed		
Relatives	Prevalence of CP (per 1000)	Relatives	Prevalence of CP (per 1000)	Relative risk (95% CI)
Twin population*	228/45 116 (5.1)	Proband-wise concordance rate*	18/228 (78.9)	15.6 (9.8 to 24.8)
Full siblings of unaffected	1929/1 226 413 (1.6)	Full siblings of affected	30/2014 (14.9)	9.2 (6.4 to 13.1)†
Offspring of unaffected	813/622 480 (1.3)	Offspring of affected	2/237 (8.5)	6.5 (1.6 to 25.6)
Half siblings of unaffected	762/354 163 (2.2)	Half siblings of affected	5/774 (6.5)	3.0 (1.1 to 8.6)‡
Nieces/nephews of unaffected	1930/1 342 559 (1.4)	Nieces/nephews of affected	3/2360 (1.3)	0.9 (0.3 to 2.7)
First cousins of unaffected	8472/5 156 811 (1.6)	First cousins of affected	23/9157 (2.5)	1.5 (0.9 to 2.7)

* See full paper for details.

†Adjusted for maternal age at birth of older sibling (<20, 20-24, 25-29, 30-34, ≥35), maternal educational level (below high school, high school, above high school), and period of first birth (1967-71, 1972-77, 1978-84, 1985-91, 1992-2002).

‡Adjusted for parental age at birth of older sibling (as above for mothers, extended to 35-39, 40-44, ≥45 for fathers), parental educational level (below high school, high school, above high school), and period of first birth (as above).