Use of placebo controls in the evaluation of surgery: systematic review

Karolina Wartolowska,[1 2] Andrew Judge,[1 2 3] Sally Hopewell,[2 4] Gary S Collins,[2 4] Benjamin J F Dean,[1 2] Ines Rombach,[1 2] David Brindley,[1 2 5 6] Julian Savulescu,[7] David J Beard,[1 2 8] Andrew J Carr[1 2 8]

[1]National Institute of Health Research Musculoskeletal Biomedical Research Unit, Oxford, UK
[2]Botnar Institute of Musculoskeletal Sciences, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford OX3 7LD, UK
[3]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, UK
[4]Centre for Statistics in Medicine, University of Oxford, Oxford, UK
[5]The Oxford—UCL Centre for the Advancement of Sustainable Medical Innovation, University of Oxford, Oxford, UK
[6]Harvard Stem Cell Institute, Holyoke Centre, Cambridge, MA, USA
[7]Oxford Uehiro Centre for Practical Ethics, University of Oxford, Oxford, UK
[8]Surgical Intervention Trials Unit (SITU), RCS Surgical Trials Unit, Botnar Institute of Musculoskeletal Sciences, Oxford, UK
Correspondence to: K Wartolowska karolina.wartolowska@ndorms.ox.ac.uk

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STUDY QUESTION

Should placebo controls be used in the evaluation of surgical interventions?

SUMMARY ANSWER

Placebo controlled surgical trials are highly informative and should be considered for selected procedures.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Surgical randomised clinical trials incorporating a placebo arm are rare but this review shows that results of many of the trials provide clear evidence against continued use of the investigated surgical procedures, and in well designed studies the risks of adverse effects are small and the placebo is safer than surgery.

Selection criteria for studies

We carried out a systematic review of randomised clinical trials that compared surgical interventions with placebo. Surgery was defined as any procedure that both changes the anatomy and requires a skin incision or use of endoscopic techniques. We searched Medline, Embase, and the Cochrane Controlled Trials Register from their inception to November 2013. The search was not limited to any particular condition, patient group, intervention, or type of outcome.

Primary outcomes

Based on the conclusions reported by the study authors, we assessed improvement in each arm and the superiority of surgery. Moreover, we used data reported in each trial to calculate the odds ratio or effect size for improvement in the surgical arm compared with the placebo arm. We estimated the harms using the reported severity of adverse events and their relevance to the trial interventions.

Main results

In 39 out of 53 (74%) trials the placebo arm showed improvement. In 27 (51%) studies the treatment effect of placebo was no different from surgery. In 26 (49%) trials, surgery was shown to be superior, but the magnitude of the effect of the surgery above placebo was generally small. Serious adverse events were reported in the surgical arm in 22 trials (42%) and in the placebo arm in 18 trials (34%); in four studies the authors did not specify in which arm the events occurred. In many trials, however, these events were unrelated to the intervention or were associated with the severity of the investigated condition.

Outcomes for improvement as reported by authors of the trials

Intervention	Superiority		Total
	No difference	Surgery	
Surgery and placebo	20	18	38
Surgery only	0	7	7
Placebo only	1	0	1
Neither surgery nor placebo	6	0	6
NA	0	1	1
Total	27	26	53

NA=outcome was prevention of death so trial cannot be interpreted in terms of improvement.

Bias and other reasons for caution

Only trials published as full text articles were included in the review, which could have resulted in selection bias. The magnitude of placebo effect could not be estimated owing to a lack of a non-treatment control group in all but one trial. The harms could not be analysed quantitatively because of limited reporting of adverse events and their relation to the particular element of the surgical procedure.

Study funding/potential competing interests

This study was funded by the National Institute for Health Research Oxford Musculoskeletal Biomedical Research Unit. Authors of this review are involved in an ongoing placebo controlled surgical randomised clinical trial (NCT01623011).

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Effect of intervention aimed at increasing physical activity, reducing sedentary behaviour, and increasing fruit and vegetable consumption in children: Active for Life Year 5 (AFLY5) school based cluster randomised controlled trial

Ruth R Kipping,[1] Laura D Howe,[1 2] Russell Jago,[3] Rona Campbell,[1] Sian Wells,[1] Catherine R Chittleborough,[4] Julie Mytton,[5] Sian M Noble,[1] Tim J Peters,[6] Debbie A Lawlor[1 2]

[1]School of Social and Community Medicine, University of Bristol, Bristol BS8 2PS, UK
[2]MRC Integrative Epidemiology Unit at the University of Bristol, Bristol BS8 2BN, UK
[3]Centre for Exercise, Nutrition and Health Sciences, School for Policy Studies, University of Bristol, Bristol BS8 1TZ, UK
[4]School of Population Health, University of Adelaide, Adelaide, SA 5005, Australia
[5]Children and Young People's Services, Bristol City Council, Bristol BS1 5RT, UK
[6]School of Clinical Sciences, University of Bristol, Bristol BS2 8DZ, UK
Correspondence to: D A Lawlor, MRC Integrative Epidemiology Unit at the University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK
d.a.lawlor@bristol.ac.uk

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Feature: Health related lifestyles of children: getting better? (*BMJ* 2014;348:g3025)

STUDY QUESTION

Is Active for Life Year 5 (AFLY5) an effective school based intervention to increase physical activity, reduce sedentary behaviour, and increase fruit and vegetable consumption in children?

SUMMARY ANSWER

The AFLY5 school based intervention is not effective at increasing levels of physical activity, decreasing sedentary behaviour, and increasing fruit and vegetable consumption in primary school children.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Some evidence from mainly poor quality trials suggests that school based interventions are effective at increasing physical activity, reducing sedentary behaviour, and increasing fruit and vegetable consumption. This trial overcame the limitations of previous studies and found no evidence that the intervention was effective.

Design

This was a school based, cluster randomised controlled trial. AFLY5 was developed according to Medical Research Council guidance for complex interventions and aimed to improve healthy behaviours with minimal disruption of normal school function. It included teacher training, 16 lessons, and 10 child-parent interactive homework activities that were consistent with the UK National Curriculum. Schools allocated to control received standard teaching. Random allocation was concealed using an automated remote system. Research staff who collected outcome data from children were blind to schools' allocation.

Participants and setting

State primary schools in Bristol City and North Somerset in southwest England were eligible for inclusion. We recruited 60 schools and 2221 children.

Primary outcome(s)

The primary outcomes were accelerometer assessed minutes of moderate to vigorous physical activity per day, accelerometer assessed minutes of sedentary behaviour per day, and self reported daily consumption of servings of fruit and vegetables.

Main results and the role of chance

In the main intention to treat analysis with adjustment for baseline variables, none of the three primary outcomes differed between children in schools allocated to the AFLY5 intervention and those allocated to control schools. The intervention was effective for three out of nine secondary outcomes after we took account of multiple testing: self reported time spent in screen viewing at the weekend (−21 (95% confidence interval −37 to −4) minutes per day), self reported number of servings of snacks per day (−0.22 (−0.38 to −0.05)), and number of servings of high energy drinks per day (−0.26 (−0.43 to −0.10)) were all reduced.

Harms No harms from the AFLY5 intervention were found.

Bias, confounding, and other reasons for caution

The study design was developed to overcome known sources of bias in other randomised controlled trials in this area. Bias from self or parental reporting of physical activity was reduced by using accelerometers. Using child reported fruit and vegetable consumption may introduce bias, but this is unlikely to explain the null result. We met or exceeded the required numbers with valid data for all outcomes on the basis of previous sample size calculations. Sensitivity analyses exploring assumptions about missing data produced results consistent with the main analyses. The intervention was not implemented in full in all schools, but a per protocol analysis was also consistent.

Generalisability to other populations

These findings are generalisable to contemporary cohorts of children in developed countries receiving state primary school education.

Study funding and registration

The AFLY5 trial is funded by the UK National Institute for Health Research Public Health Research Programme (09/3005/04), which also paid the salary of SW. Trial registration number Current Controlled Trials ISRCTN50133740.

Main intention to treat analyses of effect of AFLY5 intervention on primary outcomes assessed immediately after end of intervention

	Control (reference) group		Intervention group		Main comparison between two groups (intervention *v* control)		
Outcomes	No	Mean (SD) or No (%)	No	Mean (SD) or No (%)	No	Difference in means or odds ratio (95% CI)	P value
Time spent in MVPA (min/day)	649	56.65 (23.42)	603	55.25 (22.33)	1252	−1.35 (−5.29 to 2.59)	0.50
Time spent in sedentary behaviour (min/day)	649	451.84 (65.40)	603	454.08 (66.78)	1252	−0.11 (−9.71 to 9.49)	0.98
Servings of fruit and vegetables (No/day)	1097	1.81 (1.55)	1024	1.89 (1.70)	2121	0.08 (−0.12 to 0.28)	0.42

MVPA=moderate or vigorous physical activity; No=number of participants.

The impact of NHS resource allocation policy on health inequalities in England 2001-11: longitudinal ecological study

Ben Barr,[1] Clare Bambra,[2] Margaret Whitehead[1]

EDITORIAL by Majeed and Soljak

[1]Department of Public Health and Policy, Institute of Psychology, Health and Society, University of Liverpool, Liverpool L69 3GB, UK
[2]Department of Geography, Wolfson Research Institute for Health and Wellbeing, Durham University, Stockton on Tees, UK
Correspondence to: B Barr
benbarr@liverpool.ac.uk

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STUDY QUESTION

Did the national health inequalities policy of increasing National Health Service funding to a greater extent in deprived areas in England compared with more affluent areas lead to a reduction in geographical inequalities in mortality amenable to healthcare between 2001 and 2011?

SUMMARY ANSWER

This NHS resource allocation policy was associated with a reduction in absolute health inequalities between deprived and affluent areas from causes amenable to healthcare.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The government's health inequalities resource allocation policy, introduced in 1999 for the NHS in England, led to an increase in NHS funding allocated to deprived areas compared with affluent areas. Our study indicates that between 2001 and 2011, this policy was associated with a reduction in absolute health inequalities from causes amenable to healthcare. Each £1.00 of additional NHS resource invested in the most deprived areas was associated with greater improvements in mortality amenable to healthcare than each £1.00 (€1.22; $1.70) of additional NHS resources invested in more affluent areas. This led to a narrowing of the gap between deprived and affluent areas in this health outcome.

Participants and setting

Residents of 324 local authorities in England.

Design, size, and duration

In this longitudinal ecological study we used regression analysis to investigate the association between trends in NHS funds allocated to local areas in England between 2001 and 2011 and trends in mortality amenable to healthcare (deaths from causes for which there is evidence of preventability given timely, appropriate access to high quality care) in people aged less than 75 years. We investigated whether this association differed by level of baseline deprivation and the extent that this explained trends in inequalities in mortality amenable to healthcare.

Main results and the role of chance

Each additional £10m of resources allocated to deprived areas was associated with a reduction in 4.0 deaths in men per 100 000 population (95% confidence interval 3.1 to 4.9) and 1.8 in women per 100 000 (1.1 to 2.4). The association between absolute increases in NHS resources and improvements in mortality amenable to healthcare in more affluent areas was not significant. The absolute gap in mortality amenable to healthcare between deprived and affluent areas decreased considerably between 2001 and 2011 and our estimates indicate that 85% of this reduction could be explained statistically by the increase in NHS resources allocated to deprived areas.

Bias, confounding, and other reasons for caution

Our main outcome measure, mortality in under 75s amenable to healthcare, will under-estimate the full impact of improvements in healthcare, as it does not reflect improvements in quality of life or reductions in mortality over age 75 resulting from healthcare. We cannot rule out the possibility that our results are explained by confounding factors not controlled for in our analysis. However our finding of similar effects across different types of amenable mortality and no association with mortality from causes not considered amenable to healthcare reduces the likelihood of alternative plausible explanations not related to improved healthcare.

Generalisability to other populations

The results are generalisable and of relevance to other countries where health service access is primarily based on need (rather than ability to pay) and where policies to allocate greater resources to areas with poor health outcomes are being considered as part of a strategy to reduce health inequalities.

Study funding/potential competing interests

BB is supported by a National Institute for Health Research doctoral research fellowship (DRF-2009-02-12). MMW is supported by the DEMETRIQ project, which is funded by the Commission of the European Communities seventh framework programme (278511). We have no competing interests.

Reduction in deaths from causes amenable to healthcare, 2001-11, associated with allocation of increased NHS funds.

	Decrease in rates of deaths amenable to healthcare per 100 000 population (95% CI) for each £10m of additional NHS funds allocated	
Local authority level of deprivation	Male	Female
Most affluent (top fifth)	−0.1 (−1.1 to 0.9)	−0.4 (1.1 to −0.4)
Second fifth	0.4 (−0.6 to 1.4)	−0.01 (−0.7 to 0.7)
Third fifth	1.9 (1 to 2.8)	0.9 (0.2 to 1.6)
Fourth fifth	2.9 (1.8 to 3.9)	1.2 (0.5 to 1.9)
Most deprived (bottom fifth)	4.00 (3.1 to 4.9)	1.8 (1.1 to 2.4)
R^2	0.78	0.68

95% confidence intervals based on robust standard errors. Model based on equation 1 in supplementary appendix 2. Model adjusted for local authority, annual trend, annual unemployment rate, and annual average household income per head for each local authority.

Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry

Michael W Donnino,[1 2] Justin D Salciccioli,[1] Michael D Howell,[3] Michael N Cocchi,[1 4] Brandon Giberson,[1] Katherine Berg,[2] Shiva Gautam,[5] Clifton Callaway,[6] for the American Heart Association's Get With The Guidelines-Resuscitation Investigators

EDITORIAL by Perkins and Nolan

[1]Department of Emergency Medicine, Beth Israel Deaconess Medical Center, 1 Deaconess Road, Boston, W/CC 2, MA 02215, USA
[2]Department of Medicine, Division of Critical Care, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA
[3]Center for Quality, University of Chicago Medicine, 850 E 58th Street, Chicago, IL 60637, USA
[4]Department of Anesthesia Critical Care, Division of Neurological/Trauma/Surgical Critical Care, Beth Israel Deaconess Medical Center, 1 Deaconess Road, Boston, MA 02215, USA
[5]Department of Medicine, Beth Israel Deaconess Medical Center, 1 Deaconess Road, Boston, MA 02215, USA
[6]Department of Emergency Medicine, University of Pittsburgh, 3600 Forbes Avenue, Iroquois Building, Suite 400A, Pittsburgh, PA 15261, USA
Correspondence to: M W Donnino, Department of Emergency Medicine, Beth Israel Deaconess Medical Center, 1 Deaconess Road, WCC2, Boston, MA 02215
mdonnino@bidmc.harvard.edu

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STUDY QUESTION

Does the timing of administration of epinephrine (adrenaline) influence outcomes in patients who experience cardiac arrest with a non-shockable rhythm in hospital?

SUMMARY ANSWER

In patients with in-hospital cardiac arrest with a non-shockable rhythm, early administration of epinephrine is associated with improved outcomes including survival to hospital discharge and neurologically intact survival.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Cardiopulmonary resuscitation and intravenous epinephrine are the mainstay of treatment in advanced resuscitation protocols for patients with non-shockable cardiac arrest, yet the effect of epinephrine on outcomes after the event is unclear. This study found that earlier administration of epinephrine during resuscitation is associated with improved probability of survival to hospital discharge.

Participants and setting

Data were collected in the Get With The Guidelines-Resuscitation database (formerly National Registry of Cardiopulmonary Resuscitation, NRCPR), which contains prospective data from 570 American hospitals. The main study population comprised 25 095 adult patients who experienced a cardiac arrest with a non-shockable rhythm (pulseless electrical activity or asystole) during their hospital stay. The mean age was 72, and 57% were men.

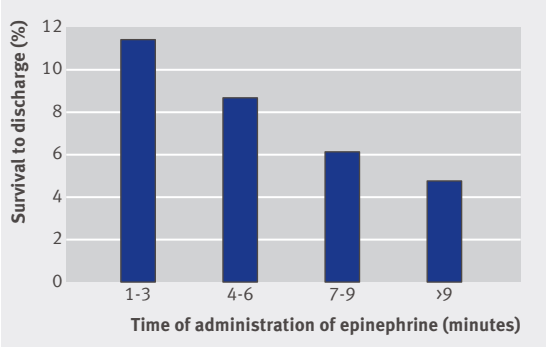
Design, size, and duration

We performed a post hoc analysis of prospectively collected data in a large multicenter registry of in-hospital cardiac arrests collected from 1 January 2000 to 19 November 2009. The exposure of interest was the time to administration of epinephrine recorded as the interval, in minutes, between recognition of the cardiac arrest and the first administered dose of epinephrine. We assessed the association between the exposure and outcomes using multivariable logistic regression. The primary outcome was survival to hospital discharge. Secondary outcomes included sustained return of spontaneous circulation, 24 hour survival, and survival with favorable neurologic status at hospital discharge.

Main results and the role of chance

Median time to administration of the first dose of epinephrine was three minutes (interquartile range 1-5 minutes). There was a stepwise decrease in survival with increasing interval of time to epinephrine (analyzed by three minute intervals): adjusted odds ratio were 1.0 for 1-3 minutes (reference group); 0.91 (95% confidence interval 0.82 to 1.00; P=0.055) for 4-6 minutes; 0.74 (0.63 to 0.88; P<0.001) for 7-9 minutes; and 0.63 (0.52 to 0.76; P<0.001) for >9 minutes. There was a similar stepwise effect across all outcome variables. In the sensitivity analyses with adjustment for delays in initiation of cardiopulmonary resuscitation, time to epinephrine administration remained independently associated with survival to hospital discharge after multivariable adjustments.

Probability of survival to hospital discharge with delays in time to epinephrine



Bias, confounding, and other reasons for caution

We attempted to control for confounding factors through multivariable adjustments for several factors that could influence survival after cardiac arrest. We performed several sensitivity analyses to deal with potential confounding from delays in initiation of cardiopulmonary resuscitation. Additional confounding that might have influenced our results could include the fact that we are unable to ascertain the specific reasons for delays in the arrival of advanced resuscitation teams. Further, while previous studies suggest that the quality of cardiopulmonary resuscitation affects outcomes after cardiac arrest, the nature of the registry data used in this investigation meant that we could not assess quality.

Generalizability to other populations

Whether an association between timing of epinephrine and survival exists in individuals with cardiac arrest with shockable rhythm in hospital or in individuals with cardiac arrest outside hospital is unknown. The effect of timing of administration of epinephrine might be different in these other populations, particularly those with shockable rhythm, given the imperative for early defibrillation.