Post-admission outcomes of participants in the PARAMEDIC trial: a cluster randomised trial of mechanical or manual chest compressions

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Abstract

Background: The PARAMEDIC cluster randomised trial evaluated the LUCAS mechanical chest compression device, and did not find evidence that use of mechanical chest compression led to an improvement in survival at 30 days. This paper reports patient outcomes from admission to hospital to 12 months after randomisation.

Methods: Information about hospital length of stay and intensive care management were obtained through linkage with Hospital Episode Statistics and the Intensive Care National Audit and Research Centre. Patients surviving to hospital discharge were approached to complete questionnaires (SF-12v2, EQ-5D, MMSE, HADS and PTSD-CL) at 90 days and 12 months. The study is registered with Current Controlled Trials, number ISRCTN08233942.

Results: 377 patients in the LUCAS arm and 658 patients in the manual chest compression were admitted to hospital. Hospital and intensive care length of stay were similar. Long term follow-up assessments were limited by poor response rates (53.7% at 3 months and 55.6% at 12 months). Follow-up rates were lower in those with worse neurological function. Among respondents, long term health related quality of life outcomes and emotional well-being was similar between groups. Cognitive function, measured by MMSE, was marginally lower in the LUCAS arm mean 26.9(SD 3.7) compared to control mean 28.0(SD 2.3), adjusted mean difference -1.5 (95% CI -2.6 to – 0.4).

Conclusion: There were no clinically important differences identified in outcomes at long term follow-up between those allocated to the mechanical chest compression compared to those receiving manual chest compression.

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Background

High quality chest compressions are associated with improved outcomes from cardiac arrest.[1-3] However, maintaining high quality chest compressions is physically challenging[4] so the concept of a mechanical chest compression device, which automates the process of chest compressions, is attractive.[5] The out of hospital, randomised assessment of a mechanical chest compression device (PARAMEDIC) trial was a cluster randomised open-label clinical effectiveness trial which compared mechanical chest compressions, delivered by the LUCAS-2 device (Physiocontrol, Lund) to manual chest compressions (control) delivered by National Health Service ambulance personnel. The initial findings of the trial have been previously reported.[6,7] The study did not find an advantage to LUCAS chest compressions for the rate of return of spontaneous circulation, (LUCAS 32% vs control 31%, adjusted OR (adjusted odds ratio ((aOR)) 1.0 (95% confidence interval 0.9–1.1)), survived event (LUCAS 23% vs control 23%, aOR 1.0 (0.8–1.1)) or 30-day survival, (LUCAS 6% vs control 7%, aOR 0.9 (0.6–1.2)). However slightly more patients in the LUCAS arm had an unfavourable neurological outcome compared to those receiving manual chest compressions (5% vs 6% respectively, aOR 0.7 (0.5-1.0)).

Most previous randomised controlled trials in out of hospital cardiac arrest have focused on short term outcomes (return of spontaneous circulation, survival to discharge).[8] Gross neurological function is usually measured with tools such as Cerebral Performance Score (CPC) and modified Rankin Scale (mRS). However, these tools may be insensitive to some of the more subtle, yet important longer term neurocognitive and functional impairments experienced by survivors of cardiac arrest.[9-11] The spectrum of impairment of health related quality of life following cardiac

arrest includes memory and cognitive dysfunction, affective disorders and post-traumatic stress disorder (PTSD).[10,12]

This paper extends the findings from the original trial by reporting on longer term outcomes amongst those who survived beyond hospital discharge. In addition, through linkage with national administrative data, hospital and intensive care unit length of stay, mode of death and organ donation rates after death are presented.

Data and Methods

The PARAMEDIC trial examined the effectiveness of LUCAS-2, a mechanical cardiopulmonary resuscitation (CPR) device, in 4471 out-of-hospital cardiac arrest patients compared to standard manual CPR. The study was designed as a cluster randomised trial, whereby the ambulance vehicles were randomised to carry the LUCAS CPR device (intervention) or not (control). Full details of study design are presented in the trial protocol, which has been published previously.[13] In brief, adults who sustained out of hospital cardiac arrest, where resuscitation was attempted by ambulance personnel and were attended by a trial vehicle were eligible for inclusion. Those with cardiac arrest caused by trauma or with known or clinically apparent pregnancy were excluded. The primary outcome (30-day survival) and some of the secondary outcomes (survived event, survival to discharge, neurological status and survival at 3 and 12 months) have been previously reported).[6] This study reports the pre-defined secondary outcomes of health-related quality of life, cognitive function, anxiety and depression, post-traumatic stress, hospital and intensive care length of stay. These outcomes are also presented in the in-depth trial report published as a Heath Technology Assessment Monograph.[7] Post-hoc additional analyses included reporting intensive care and hospital free days, mode of death and organ donation rates after death.

Linkage with Health & Social Care Information Centre (HSCIC) and the Intensive Care National Audit Research Centre (ICNARC)

The UK Health & Social Care Information Centre (HSCIC) and Intensive Care National Audit & Research Centre (ICNARC), were contacted for the hospital data of patients who survived long enough to be admitted to hospital. This analysis was based on the combination of the original trial, and linked HSCIC and ICNARC data. Approvals were obtained from the Coventry and Warwickshire Research Ethics Committee, HSCIC Data Access Advisory Group (DAAG) and ICNARC.

The trial recruitment was run between April 15, 2010, and June 10, 2013. Patient flow was shown in the CONSORT diagram (Figure 1). Of the 4471 randomised patients, 2695 (951 or 35.3% in LUCAS) were not known to be deceased at emergency department. No patient recruited after March 2013 were linked to HSCIC because the 2013-14 data were not available before our linkage application. Therefore, 2398 (843 or 35.2% in LUCAS) were considered eligible for linkage.

Information on hospital length of stay was provided by Hospital Episodes Statistics (HES) admitted and A&E datasets. Approximately 40-50% of patients admitted to hospital after cardiac arrest are admitted to intensive care.[14] ICNARC provided data for intensive care duration, survival, temperature management, organ donation and withholding of treatment information.

HES admitted patient care data were used to calculate hospital length of stay and survival to hospital discharge, with supplementary discharge and death data collected in the trial. Hospital length of stay was defined as days between cardiac arrest and discharge from or death in hospital. ICU length of stay was defined as days between ICU admission and discharge from or death in ICU. Patients who did not achieve sustained ROSC at hospital handover were assumed to have a hospital stay of zero days. Intensive care-free days was defined as the number of days that a patient was alive and not requiring intensive care during the first 30 days after the cardiac arrest. Hospital-free survival days was defined as the number of days alive post-hospital discharge during the first 30 days after the cardiac arrest. Re-admission to hospital or ICU was not counted.

Follow-up questionnaires.

Patients who were alive and consented to long-term follow-up were contacted by letter at the relevant follow-up point. Non-responders were sent a 2nd letter followed by a telephone call before being declared lost to follow-up. Participants were asked to self-complete several patient-reported outcome measures including two generic measures of health-related quality of life (HRQoL) - Short-Form 12-item Health Survey version 2 (SF-12v2)[15] and the single item EuroQoL-Visual Analogue Scale (EQ-VAS)[16] – and domain-specific measures of emotional well-being - Hospital Anxiety and Depression Scale (HADS), Mini-Mental State Examination (MMSE)[17] and the PTSD Civilian Checklist (PTSD-CL)[18]. Questionnaires were returned by post to the trial co-ordinating centre at Warwick Clinical Trials Unit.

Analysis

Patients' outcomes were compared by treatment arm, using fixed-effect logistic and linear regression models to obtain unadjusted and adjusted odds ratios (OR) or mean difference and 95% confidence intervals (CI). The pre-specified covariates used in the adjusted models were age, sex, response time (time interval from 999 call to arrival of the trial vehicle), bystander CPR, and initial rhythm. We attempted adjusting for the clustering design using multilevel logistic models (using the GLIMMIX procedure with logit link function based on the binomial distribution). Because of the extremely low survival rates in each cluster (vehicle), the multilevel models could not be fitted with the vehicle random effect since this effect was not estimable. For this reason, we assumed that the intra-cluster correlation coefficient was negligible (0.001) and ordinary logistic regressions were fitted. Analyses used complete cases only, with no imputation. Intention to treat approach was used for all analyses, which were conducted in SAS v9.3 and v9.4 (Cary, NC, USA).

Results

The trial ran between April 15, 2010, and June 10, 2013 (which included 12 months' follow-up). During this time 4471 patients were enrolled of which 1652 were allocated to receive LUCAS and 2819 manual chest compression of which 1099 and 1868 were transferred to hospital. 377 patients in the LUCAS arm and 658 patients in the manual chest compression survived the event (survived beyond hospital admission (figure 1). Data linkage between Hospital Episode Statistics and those who survived to hospital admission was successful for 264, 70% (LUCAS) and 507, 77% (manual chest compression group) and ICNARC critical care, 147 ((LUCAS) and 260 (control).

Hospital stay characteristics

For patients who survived to hospital discharge, the unadjusted hospital length of stay was 19.7 (LUCAS) and 14.5 (control) days, with an adjusted mean difference of 2.5 days (95% CI -4.9, 9.9). For non-survivors, the unadjusted hospital length of stay was 0.7 days (LUCAS) and 0.6 days (control), with an adjusted mean difference of -0.01 day (-0.5, 0.5). The number of days alive and free from intensive care in the first 30 days was 1.8 and 2.1 respectively (adjusted mean difference -0.5 (-0.9, -0.1)). Unadjusted hospital free survival days was 0.7 (LUCAS) and 1.0 (control) (adjusted mean difference -0.4 (-0.6, -0.1)).

Intensive care stay characteristics

Table 1 summarises key characteristics of the intensive care stay of patients with matched ICNARC records. The majority of patients had temperatures consistent with the application of targeted temperature management (TTM), although this should be interpreted with caution due to substantial missing data. Overall survival was similar between arms (42.9% LUCAS, 41.5% control, aOR 1.1 (95%CI 0.7-1.8). Treatment was withdrawn in approximately one third in each arm. Small number of patients underwent heart beating solid organ donation and non-heart beating solid organ donation.

3 and 12 month questionnaire follow-up

The 3 and 12 month questionnaire follow up rates for patients surviving to 3 and 12 months were 53.7% and 55.6% respectively. Table 2 reports the follow up rates according to CPC category. Follow-up rates were lower in those with worse neurological outcomes.

At the three month follow-up (Table 3), SF-12 mental and physical component scores (MCS, PSC), and EQ-VAS scores were slightly lower in the LUCAS-2 group than the control group. The confidence intervals for the adjusted differences crossed zero.

At 12-month follow-up (Table 4), all of the results were in the same direction, but only the Mini mental state examination showed significant difference between treatment arms (95% confidence intervals excluded zero).

Discussion

This study evaluated longer term outcomes amongst participants in the cluster randomised PARAMEDIC trial. The study found no significant differences in intensive care outcomes when comparing manual and mechanical (LUCAS) CPR. However, hospital-free survival was slightly reduced in patients assigned to the LUCAS arm compared to those in the standard compression arm, after adjustment for covariates. At twelve months follow up, physical function (SF-12), global quality of life (EQ-VAS) and depression (Hospital Anxiety Depression Scale) was similar in patients in the LUCAS arm compared to standard chest compressions. Whilst cognitive function (mini-mental state examination) score was slightly worse (-1.5 (95% CI -2.6, -0.4) the difference fell below the threshold of a clinically important difference (3.72 points).[19]

Mechanical chest compression devices have been evaluated in five randomised controlled trials, which enrolled over 10,000 participants.[20] Meta-analyses of these trials results found no advantage to mechanical chest compression in survival to discharge/30 days (average OR 0.89, 95% CI 0.77-1.02) and survival with good neurological outcome (average OR 0.76, 95% CI 0.53-1.11).[20] These findings informed the International Liaison Committee for Resuscitation, Consensus on Science and Treatment Recommendation which suggests against the routine use of automated mechanical chest compression devices to replace manual chest compressions.[21] This study is the first of the mechanical chest compression device studies to explore the long-term outcomes and health related quality of life in this cohort of patients.

Compared to the UK adult population norms,[22] survivors at 12-months post-arrest have a significantly reduced quality of life across all HRQOL measures; this was particularly reduced for the SF-12 physical component scores where the reduction was greater than half a standard deviation, and hence of potential clinical relevance.[23] This contrasts with reports of comparable levels of mental and physical health on the SF-12 at 12-months for Australian survivors of OHCA and the general population.[24,25] Although SF-12 MCS scores for the current study are comparable with those of the Australian cohort, PCS scores are significantly reduced. Both physical and mental health scores are slightly reduced when compared to those reported in a Dutch cohort of survivors at 6-12 months post arrest.[26] A similarly reduced quality of life in survivors, as assessed by the EQ-5D-3L index, has been previously reported for this cohort.[7,27] When compared to the UK population norm, the reduction ranged between 0.07 and 0.09 in the manual CPR group and between 0.21 and 0.22 in the LUCAS-2 group (at 3 and 12-months respectively). A reduction greater than 0.18 is reported to be of clinical relevance.[28]

These findings are consistent with the observation in the main PARAMEDIC trial of marginally worse neurological outcomes 3 months after cardiac arrest reported previously (Cerebral Performance Category 1-2, 5% LUCAS versus 6% control [adjusted OR 0.72 (0.52-0.99)])[6,7]. This finding was

unexpected although not unprecedented as the ASPIRE trial which studied the Autopulse mechanical chest compression device was terminated early due to worse neurological outcomes in the intervention group.[29] Physiologically, mechanical chest compression devices provide consistent quality CPR.[30] Animal[31] and human studies [32] report improved cortico-cerebral perfusion and cerebral oxygenation. A possible explanation includes interruptions to chest compressions caused by the time taken to deploy the device. The manufacturer recommends a two-stage approach to device deployment. Stage one involves deployment of the back plate. Manual CPR is then restarted prior to pausing to deploying the device, preparing the suction cup and starting mechanical CPR. Analysis of transthoracic impedance data suggests stage one takes approximately 9 seconds (inter-quartile range 5.5–14.5) and stage two 32.5 seconds (inter-quartile range 25–61).[33] With focused team training it possible to reduce the duration for deployment to 13 seconds.[34] This is likely to be particularly important when, as seen in our study, the exposure of paramedics to cardiac arrest is low (approximately 2 arrests per year).[6]

The concept of disease free survival (number of days alive during a specific time period, free from disease) has been used widely in studies enrolling critically ill patients. Ventilator free days has become popular as an intermediate outcome in trials of treatments for the acute respiratory distress syndrome.[35] Its use is favoured for the improved statistical efficiency of a continuous as opposed to a dichotomous (alive / dead) outcome [35] and its patient centredness.[36] Nichol was one of the first to use hospital free survival in a large cluster randomised trial comparing continuous chest compressions with positive pressure ventilation to standard CPR.[37] That study concluded no overall difference in survival (9% compression only, 9.7% interrupted chest compression, difference, −0.7 % 95% CI −1.5 to 0.1). A small difference in hospital free survival (−0.2 days; 95% CI, −0.3 to −0.1) was however observed. The present trial also found a very small difference in hospital free survival, favouring manual chest compressions. However it is likely this falls below the threshold of a clinically important difference. There may be value in further research to gain a better understanding of the characteristics, interpretation and statistical analysis of hospital free survival.[38]

Strengths of this study include the prospective, randomised design, its independence from commercial sponsorship[39] and focus on long term outcomes. Nevertheless, this and similar studies face limitations which require the results to be interpreted with caution. All longer term follow-up studies are limited by the effects of survivor bias i.e. only those alive are eligible for inclusion in follow-up. This is further compounded in the present study, as those with the worse neurological outcomes were less likely to participate in follow-up (Table 2) which risks introducing outcome reporting bias. Accepting these limitations, the overall follow-up rate amongst survivors was on average 55%. This is within the range of rates reported in other studies (range 25%-86%).[40-42] These high levels of missing data risk underestimating or potentially misleading the full impact of cardiac arrest amongst survivors.

Conclusion:

There were no clinically important differences identified in outcomes at long term follow-up between those allocated to the mechanical chest compression compared to those receiving manual chest compression.

Collaborators

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Declaration of interests

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Table 1: Outcomes by treatment arm in patients with ICNARC data.

	LUCAS (N=147)	Control (N=260)	Odds ratio or Difference (95% CI); unadjusted	Odds ratio or Difference (95% CI); adjusted*
ICU survival				
Survived at ICU	63 (42.9%)	108 (41.5%)	1.1 (0.7, 1.6)	1.1 (0.7, 1.8)
Deceased at ICU	84 (57.1%)	152 (58.5%)	1	1
Length of stay days				
Mean (SD)	7.3 (20.3)	4.5 (5.1)	2.9 (0.3, 5.5)	3.4 (0.6, 6.3)
Median (IQR)	3.0 (6.0)	3.0 (4.0)		
Missing	0	0		
Low central temperature less than 34 degrees				
Yes	55 (37.4%)	80 (30.8%)	1.8 (0.8, 4.2)	2.1 (0.8, 5.6)
No	9 (6.1%)	24 (9.2%)	1	1
Missing	83 (56.5%)	156 (60.0%)		
Treatment withheld/withdrawn**				
Both withheld then withdrawn	10 (6.8%)	13 (5.0%)	1.3 (0.5, 3.0)	1.2 (0.5, 3.1)
Withheld	2 (1.4%)	2 (0.8%)	1.6 (0.2, 11.8)	1.7 (0.2, 13.8)
Withdrawn	41 (27.9%)	92 (35.4%)	0.7 (0.5, 1.1)	0.7 (0.4, 1.1)
Neither	94 (63.9%)	153 (58.8%)	1	1

Organ donation				
Heartbeating solid organ donor	7 (4.8%)	6 (2.3%)	2.2 (0.7, 6.6)	4.0 (1.0,15.2)
Non-heartbeating solid organ donor	6 (4.1%)	9 (3.5%)	1.2 (0.4, 3.6)	1.2 (0.4, 4.0)
Tissue donor only	1 (0.7%)	7 (2.7%)	0.3 (<0.1, 2.2)	0.4 (<0.1, 3.1)
No solid organs or tissues donated	70 (47.6%)	129 (49.6%)	1	1
Missing	63 (42.9%)	109 (41.9%)		

*Note: *: Odds ratio and mean difference are adjusted for age, sex, rhythm, bystander CPR and response time; ** Withholding treatment is defined as a decision not to start or increase a life-sustaining intervention and withdrawing treatment as a decision to actively stop a life-sustaining intervention that is presently being given.*

Table 2: 3 and 12 month questionnaire follow-up rates

	LUCAS				Manual chest compression			
3 month CPC categories	CPC 1	CPC 2	CPC 3	CPC 4	CPC 1	CPC 2	CPC 3	CPC 4
Number alive at 3 months	67	10	14	2	153	15	10	1
3 month questionnaire response	55.2%	50.0%	28.6%	50.0%	61.4%	26.7%	10.0%	0.0%
Alive at 12 months*	64 (95.5%)	10 (100.0%)	11 (78.6%)	1 (50.0%)	148 (96.7%)	13 (96.7%)	9 (90.0%)	1 (100.0%)
12 month questionnaire response	60.9%	60.0%	27.3 %	0.0%	60.1%	30.8%	20.0%	0.0%

Note: * percentage is calculated as number of alive at 12 months/number of alive at 3 months.

Table 3 Outcome at 3 months for the SF-12v2 and EQ-VAS.

Patient-reported outcomes[a]		LUCAS-2 n=47	CONTROL N=99	Difference (95% CI); unadjusted	Difference (95% CI); adjusted*
Generic health-related quality of life					
SF-12 PCS	*Mean (SD)*	38.9 (11.5)	41.7 (10.9)	-2.8 (-6.7, 1.1)	-3.0 (-7.0, 1.1)
	Median (IQR)	40.8 (32.1, 48.0)	42.6 (34.7, 49.4)		
	missing	2	2		
SF-12 MCS	*Mean (SD)*	47.3 (13.4)	48.9 (10.5)	-1.6 (-5.6, 2.5)	-1.5 (-5.5, 2.6)
	Median (IQR)	51.7 (38.2, 57.3)	50.2 (42.1, 57.2)		
	missing	2	2		
EQ-VAS	*Mean (SD)*	63.8 (23.5)	72.0 (18.0)	-8.2 (-15.1, -1.3)	-6.8 (-13.7, 0.1)
	Median (IQR)	65.0 (50.0, 80.0)	75.0 (64.0, 85.0)		
	missing	0	0		

*Note: *: Mean difference are adjusted for age, sex, rhythm, bystander CPR and response time.*

Footnote:

a SF-12 Physical Component Score (PCS) and Mental Component Scores (MCS) are scored 0-100; higher scores represent

better health states. The UK adult population mean or normative value is 50 (SD 10) for both PCS and MCS [Layte and

Jenkinson, 2001) (https://campaign.optum.com/optum-outcomes/what-we-do/health-

surveys.html?gclid=CLGxgvym9tACFU-T7QodWoQHkg).

EQ-VAS is scored 0 to 100, where 100 represents the best quality of life. The UK adult population mean or normative

value is 82.48 (0.292) for the EQ-VAS.

Table 4 Patient-reported outcomes at 12 months for- the SF-12v2, EQ-VAS and MMSE.

Patient-reported outcomes[a]		LUCAS-2 N=48	CONTROL N= 95	Difference (95% CI); unadjusted	Difference (95% CI); adjusted*
Generic health-related quality of life					
SF-12 PCS	*Mean (SD)*	40.1 (12.7)	43.8 (10.7)	-3.8 (-7.8, 0.2)	-3.5 (-7.4, 0.4)
	Median (IQR)	40.7 (30.8, 51.0)	44.9 (36.1, 52.5)		
	missing	1	2		
SF-12 MCS	*Mean (SD)*	47.5 (11.5)	49.4 (11.8)	-1.8 (-5.9, 2.3)	-1.5 (-5.5, 2.5)
	Median (IQR)	48.9 (42.9, 55.3)	50.8 (42.7, 59.1)		
	missing	1	2		
EQ-VAS	*Mean (SD)*	68.3 (22.0)	75.0 (17.4)	-6.7 (-13.3, -0.07)	-6.4 (-13.1, 0.3)
	Median (IQR)	72.0 (54.5, 87.5)	80.0 (64.0, 90.0)		
	missing	0	0		
Cognitive function					
Mini mental state examination	*Mean (SD)*	26.9 (3.7)	28.0 (2.3)	-1.12 (-2.2, -0.08)	-1.5 (-2.6, -0.4)
	Median (IQR)	28.0 (27.0, 29.0)	29.0 (27.0, 30.0)		
	missing	1	1		
Emotional well-being					
HADS: anxiety	*Mean (SD)*	6.7 (4.8)	5.7 (4.2)	0.9 (-0.6, 2.5)	0.6 (-0.9, 2.1)
	Median (IQR)	6.0 (3.0, 10.0)	6.0 (2.0, 8.0)		
	missing	0	0		
HADS: depression	*Mean (SD)*	5.8 (4.4)	4.4 (3.5)	1.42 (0.09, 2.8)	1.1 (-0.2, 2.5)

	Median (IQR)	5.0 (2.0, 9.0)	4.0 (1.0, 7.0)		
	missing	0	0		
PTSD-CL	Mean (SD)	32.0 (12.9)	30.2 (11.0)	1.8 (-2.4, 5.9)	1.6 (-2.6, 5.7)
	Median (IQR)	28.0 (22.0, 36.0)	28.0 (20.0, 38.0)		
	missing	3	2		

Note: *: Mean difference are adjusted for age, sex, rhythm, bystander CPR and time interval from 999 call to arrival of the trial vehicle.

Footnote:

a SF-12 Physical Component Score (PCS) and Mental Component Scores (MCS) are scored 0-100; higher scores represent better health states. The UK adult population mean or normative value is 50 (SD 10) for both PCS and MCS [Layte and Jenkinson, 2001) (https://campaign.optum.com/optum-outcomes/what-we-do/health-surveys.html?gclid=CLGxgvym9tACFU-T7QodWoQHkg**).**

EQ-VAS is scored 0 to 100, where 100 represents the best quality of life. The UK adult population mean or normative value is 82.48 (0.292) for the EQ-VAS (Kind et al, 1999a,b).

MMSE is scored 0-30, where higher scores represent better health.

HADS – Anxiety and Depression Scales are scored 0-21, where lower scores represent better levels of health.

PTSD-CL is scored 17-85, where lower scores represent better levels of health.

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