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RESEARCH

Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: meta-analysis and systematic review

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ABSTRACT

Objective To summarise the evidence for early extubation with immediate application of non-invasive ventilation compared with continued invasive weaning on important outcomes in intubated adults with respiratory failure.

Design Systematic review and meta-analysis of randomised and quasi-randomised controlled trials.

Setting Intensive care units.

Participants Critically ill adults receiving invasive ventilation.

Study selection criteria We searched Medline, Embase, and CENTRAL, proceedings from four conferences, and reference lists of relevant studies to identify relevant trials. Two reviewers independently selected trials, assessed trial quality, and abstracted data.

Results We identified 12 trials enrolling 530 participants, mostly with chronic obstructive pulmonary disease. Compared with invasive weaning, non-invasive weaning was significantly associated with reduced mortality (relative risk 0.55, 95% confidence interval 0.38 to 0.79), ventilator associated pneumonia (0.29, 95% 0.19 to 0.45), length of stay in intensive care unit (weighted mean difference −6.27 days, −8.77 to −3.78) and hospital (−7.19 days, −10.80 to −3.58), total duration of ventilation, and duration of invasive ventilation. Non-invasive weaning had no effect on weaning failures or weaning time. Benefits on mortality and weaning failures were non-significantly greater in trials that exclusively enrolled patients with chronic obstructive pulmonary disease versus mixed populations.

Conclusions Current trials in critically ill adults show a consistent positive effect of non-invasive weaning on mortality and ventilator associated pneumonia, though the net clinical benefits remain to be fully elucidated. Non-invasive ventilation should preferentially be used in patients with chronic obstructive pulmonary disease in a highly monitored environment.

INTRODUCTION

Invasive ventilation maintains a patent airway but when used over a prolonged period of time might lead to ventilator associated pneumonia.[1] Non-invasive ventilation provides an alternative method of supporting a patient's respiration by using positive pressure ventilation with either an oronasal, nasal, or total face mask at the patient-ventilator interface. Non-invasive ventilation preserves the patient's ability to speak and cough[2] and has been shown to reduce complications related to intubation, especially ventilator associated pneumonia.[3 4]

To mitigate the effect of complications associated with protracted invasive ventilation, investigators have explored the role of non-invasive ventilation in weaning patients from invasive ventilation. In light of new evidence, we critically appraised, summarised, and updated current work on the effect of non-invasive weaning compared with invasive weaning on the primary outcome of mortality and secondary outcomes including ventilator associated pneumonia, length of stay in intensive care and in hospital, and duration of ventilator support in critically ill mechanically ventilated adults.

METHODS

Data sources and searches

We updated a previously conducted search of Medline, Embase, and the Cochrane Central Register of Controlled Trials. Two reviewers screened citation titles and abstracts independently. One reviewer updated manual searches of published abstracts from intensive care conference proceedings. We reviewed bibliographies of all retrieved articles and contacted authors of included studies to identify unpublished studies.

Study selection

We included randomised trials that enrolled adults with respiratory failure who required invasive mechanical ventilation for at least 24 hours. The trials examined extubation with immediate application of non-invasive ventilation compared with continued invasive weaning. We also included quasi-randomised controlled trials—for example, those that allocated patients by hospital registry number or day of the week. Two authors independently selected articles meeting the inclusion criteria.

Data extraction and quality assessment

Two authors not blinded to the source of the reports used a standardised data abstraction form independently to abstract data regarding study methods. Additionally, we assessed features unique to the design and

implementation of weaning trials. Disagreements were resolved by consensus and arbitration with a third author.

Data synthesis and statistical analysis

When there were no compelling differences in study populations, interventions, and outcomes we pooled data across studies using random effects models. We derived summary estimates of relative risk and weighted mean difference for binary and continuous outcomes, respectively.

We determined the presence and impact of statistical heterogeneity among studies using the Cochran Q statistic and the I^2 test. In sensitivity analyses, we assessed the impact of excluding quasi-randomised trials on mortality and ventilator associated pneumonia. We planned subgroup analyses to compare the effects of non-invasive weaning on mortality and weaning failures in exclusively chronic obstructive pulmonary diseases (COPD) compared with non-COPD populations and on mortality in studies that enrolled ≥50% versus <50% patients with COPD. We used random effects models for sensitivity and subgroup analyses and assessed for differences between subgroups in summary estimates using a z test for interaction.

We assessed for publication bias in mortality by visually inspecting the corresponding forest plot. Post hoc, we conducted additional pooled analyses of mortality at various time points to assess the robustness of the results.

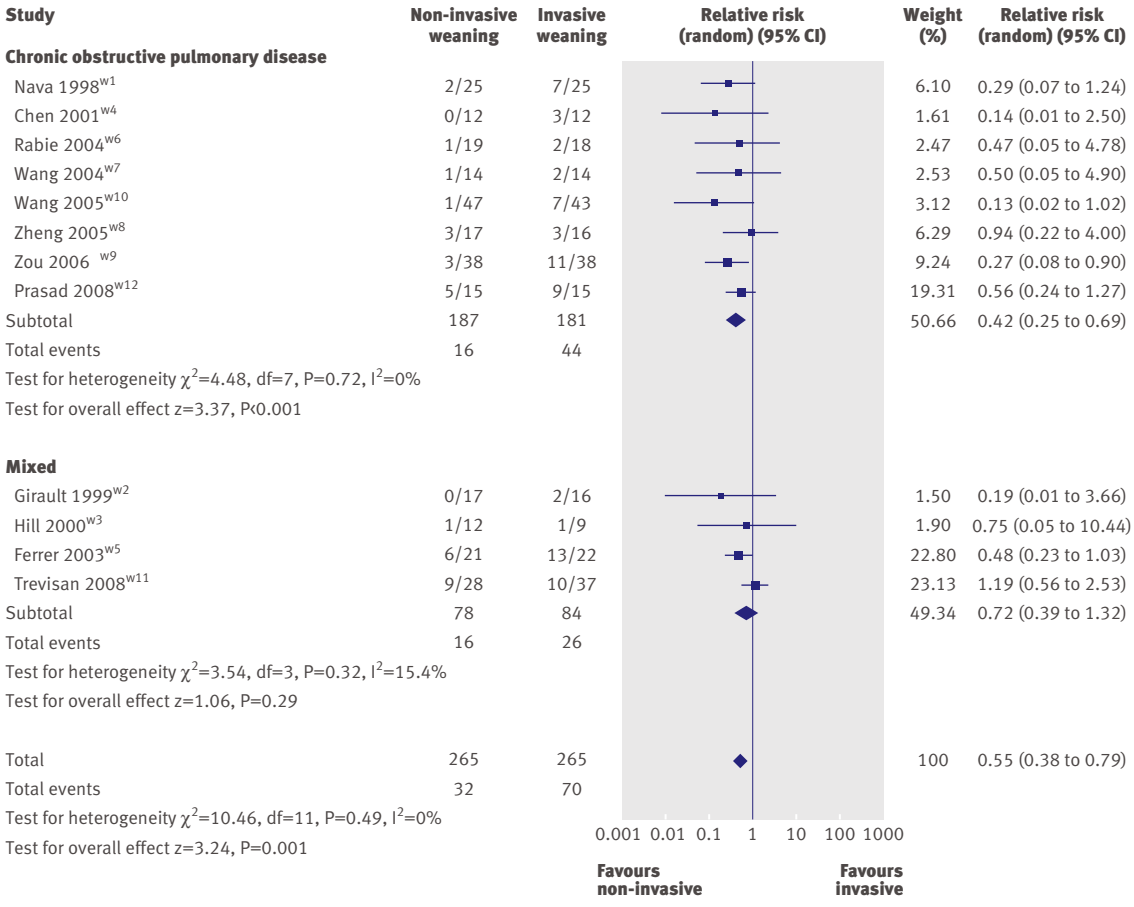
RESULTS

Trial identification

We identified 12 randomised trials,[w1-w12] including one quasi-randomised trial,[w4] that met our inclusion criteria. See bmj.com.

Initial management

Initial pre-randomisation ventilation strategies entailed volume-cycled ventilation[w1 w2 w4-w7 w9 w10 w12] predominantly, with or without the concurrent or subsequent use of pressure support. In three trials, screening for weaning eligibility occurred daily[w3 w5] ordaily after 48 hours of invasive ventilation.[w2] Alternatively, candidates for weaning were identified after at least 24 hours,[w12] 36-48 hours (including 6-8 hours of paralysis),[w1] 48 hours,[w2] 48-60 hours,[w4] 72 hours (including 6-8 hours of paralysis),[w6] or three days[w5] of invasive ventilation. Eligibility for study inclusion was based on meeting predefined criteria for readiness for weaning[w1 w2 w4 w12] and failure of either a single 30 minute,[w3 w11] one hour,[w1] or two hour[w2 w6 w12] T-piece trial, or failure of two hour T-piece trials on three consecutive days.[w5]



Effect of non-invasive and invasive weaning on mortality in critically ill adults on invasive ventilation

Four studies,[w7-w10] evaluating patients with chronic obstructive pulmonary disease with pulmonary infection, enrolled patients after control of infection was achieved[w7] or when they met pulmonary infection control criteria.[w8-w10]

Weaning

See bmj.com for details of the different weaning protocols used for invasive and non-invasive weaning in the different studies.

Quality assessment

Nine study authors provided information about quality.[w1-w3 w5 w6 w8 w9 w11 w12] Overall, the included studies were of moderate to high quality. See bmj.com.

Primary outcome: mortality

All 12 trials (530 patients) provided mortality data, reported at 30 days,[w12] 60 days,[w1] 90 days,[w2 w5] at hospital discharge,[w6 w9-w11] or at an undefined time.[w3 w4 w7] There was strong evidence that non-invasive weaning was associated with reduced mortality (relative risk 0.55, 95% confidence interval 0.38 to 0.79, P=0.001), with no heterogeneity (figure).

Secondary outcomes

Pooled data from 11 studies (509 patients)[w1 w2 w4 w5 w6-w12] showed that non-invasive weaning was associated with decreased ventilator associated pneumonia (relative risk 0.29, 0.19 to 0.45, P<0.001), with no heterogeneity. Nine studies provided diagnostic criteria for ventilator associated pneumonia.[w1 w4 w5 w7-w12] Meta-analyses also showed that patients undergoing non-invasive weaning had clinically and statistically reduced length of stay in intensive care (6.3 days) and hospital (7.2 days), total duration of mechanical ventilation (5.6 days), and duration of invasive ventilation (7.8 days), with significant heterogeneity. Non-invasive weaning had no effect on the duration of mechanical ventilation related to weaning or weaning failures, and no study reported on quality of life.

Adverse events

Notwithstanding few events and wide confidence intervals, the pooled results showed no difference in arrhythmias (two studies, 63 patients) or reintubation (six studies, 328 patients), and significantly fewer tracheostomies (three studies, 141 patients) with non-invasive weaning.

Sensitivity and subgroup analyses

Exclusion of a quasi-randomised trial[w4] maintained the significant reductions in mortality (relative risk 0.56, 0.39 to 0.81, P=0.002) and ventilator associated pneumonia (0.30, 0.20 to 0.47, P<0.001) in favour of non-invasive weaning. We noted a non-significant beneficial effect (z=−1.332; P=0.18) of non-invasive weaning in patients with chronic obstructive pulmonary disease (eight studies) compared with mixed populations (four studies) (0.42, 0.25 to 0.69, and 0.72, 0.39 to 1.32).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Non-invasive ventilation has been widely investigated as an initial treatment to prevent intubation and intubation related complications

Many patients with severe respiratory failure, impaired sensorium, haemodynamic instability, or difficulty clearing secretions undergo direct intubation or intubation after a failed attempt at non-invasive ventilation

WHAT THIS STUDY ADDS

Non-invasive weaning was associated with decreased mortality, ventilator associated pneumonia, length of stay in intensive care and hospital, total duration of mechanical ventilation, and duration of invasive ventilation

When we conducted a subgroup analysis evaluating studies enrolling ≥50% (10 studies) versus <50% (two studies) patients with chronic obstructive pulmonary disease, we found a significant benefit of non-invasive weaning on mortality in favour of studies enrolling predominantly patients with chronic obstructive pulmonary disease (0.43, 0.28 to 0.65, and 1.15, 0.56 to 2.37; z=−2.308; P=0.02). Similarly, we noted a non-significant but greater effect of non-invasive weaning on weaning failures in patients with chronic obstructive pulmonary disease (two studies) compared with mixed populations (two studies) (0.50, 0.22 to 1.12, and 1.28, 0.45 to 3.60; z=−1.395; P=0.16).

Publication bias

Visual inspection of a funnel plot showed asymmetry and suggested the absence of studies with non-significant results. The absence of such trials might overinflate the overall summary estimate of effect.

DISCUSSION

In critically ills adults in intensive care non-invasive weaning is associated with decreased mortality, ventilator associated pneumonia, length of stay in intensive care and hospital, total duration of mechanical ventilation, and duration of invasive ventilation. The optimal timing for transitioning patients to non-invasive ventilation for weaning remains to be determined.

Patients with chronic obstructive pulmonary disease might be ideally suited to non-invasive ventilation given its ability to offset respiratory muscle fatigue and tachypnoea, augment tidal volume, and reduce intrinsic positive end expiratory pressure.[5 6] Subgroup analyses suggested greater benefits of non-invasive weaning in patients with chronic obstructive pulmonary disease, although result of analyses of subgroup effects were predominantly non-significant.

We found that non-invasive weaning significantly reduced mortality and length of stay in intensive care and hospital consistent with (and possibly due to) the observed reduction in ventilator associated pneumonia. Direct access to respiratory secretions among invasively weaned patients, however, might have enhanced

detection of ventilator associated pneumonia in this group. Moreover, in the control groups mortality (range 11.1%[w3 w6] to 60.0%[w12]) and rates of ventilator associated pneumonia (range 6.3%[w2] to 59.1%[w5]) varied among the included trials. The small number of events in the included studies,[7] the variability in event rates in control groups, and the absence of a single adequately powered randomised controlled trial directly comparing the alternative weaning strategies limits the strength of our inferences.

The included studies varied in the methods used to identify candidates for weaning and to titrate and discontinue mechanical support. See bmj.com. While methods for identifying candidates for weaning might affect study estimates of the duration of ventilation, they represent pre-randomisation study design considerations and are less likely to result in important performance bias. Conversely, unequal or inconsistent use of weaning protocols and the frequency with which periods of spontaneous breathing (non-invasive strategy) or trials of spontaneous breathing (invasive strategy) were permitted represent important post-randomisation study design considerations that could bias estimates of the duration of ventilation in unblinded weaning trials. Overall, most trials included measures to reduce bias after randomisation and were of moderate to high quality, though variation among trials in adopting these measures limits interpretation of some of the pooled results.

Conclusion

Current trials of non-invasive weaning, while limited by inclusion of small numbers of patients mostly with chronic obstructive pulmonary disease, consistently show positive effects on mortality and ventilator associated pneumonia. If consideration is being given to weaning patients with non-invasive ventilation, we suggest that it be preferentially used in patients with chronic obstructive pulmonary disease and applied in a highly monitored environment.

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Competing interests: SPK has received an unrestricted grant from Respironics Inc to support development of a non-invasive ventilation guideline for the Canadian Critical Care Trials Group.

Ethical approval: Not required.

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Supplementary feeding with either ready-to-use fortified spread or corn-soy blend in wasted adults starting antiretroviral therapy in Malawi: randomised, investigator blinded, controlled trial

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ABSTRACT

Objective To investigate the effect of two different food supplements on body mass index (BMI) in wasted Malawian adults with HIV who were starting antiretroviral therapy.

Design Randomised, investigator blinded, controlled trial.

Setting Large, public clinic associated with a referral hospital in Blantyre, Malawi.

Participants 491 adults with BMI <18.5.

Interventions Ready-to-use fortified spread (n=245) or corn-soy blend (n=246).

Main outcome measures Primary outcomes: changes in BMI and fat-free body mass after 3.5 months. Secondary outcomes: survival, CD4 count, HIV viral load, quality of life, and adherence to antiretroviral therapy.

Results The mean BMI at enrolment was 16.5. After 14 weeks patients receiving fortified spread had a greater increase in BMI and fat-free body mass than those receiving corn-soy blend: 2.2 (SD 1.9) *v* 1.7 (SD 1.6) (difference 0.5, 95% confidence interval 0.2 to 0.8), and 2.9 (SD 3.2) *v* 2.2 (SD 3.0) kg (difference 0.7 kg, 0.2 to 1.2 kg), respectively. The mortality rate was 27% for those receiving fortified spread and 26% for those receiving corn-soy blend. No significant differences in the CD4 count, HIV viral load, assessment of quality of life, or adherence to antiretroviral therapy were noted between the two groups.

Conclusion Supplementary feeding with fortified spread resulted in a greater increase in BMI and lean body mass than feeding with corn-soy blend.

Trial registration Current Controlled Trials ISRCTN67515515.

INTRODUCTION

In sub-Saharan Africa mortality during the first months of antiretroviral therapy is high, and a low BMI is an independent risk factor for this early mortality.[1] Supplementary feeding might improve outcomes in patients receiving antiretroviral therapy because it ameliorates food insecurity. Evidence to support the effectiveness of this practice, however, is limited.[2]

The most commonly available supplementary food in food aid programmes is corn-soy blended flour, an inexpensive fortified cereal-legume combination that requires cooking and that has been widely used in Africa for decades. Corn-soy blend, however, has been associated with disappointing results in supplementary feeding programmes.[3-5] Specialised, energy dense ready-to-use fortified spreads have also been recommended for feeding wasted adults with HIV. This spread is a pre-cooked, energy dense, lipid paste made from peanuts that resists bacterial contamination.[6]

We conducted a randomised controlled trial to test the hypothesis that among wasted adults with HIV starting antiretroviral therapy, patients who receive the fortified spread will have a greater increase in BMI and fat-free body mass than those receiving corn-soy blend.

METHODS

Participants and study site

Eligible participants were all adults aged 18 or over with HIV (WHO clinical stage III or IV or any WHO stage with a CD4 count <250/mm^3) and were starting treatment with a BMI <18.5. The study took place in Blantyre, Malawi, from January 2006 to April 2007. Routine prophylaxis with co-trimoxazole before and during antiretroviral therapy had not been fully implemented at the time of the study.

Study design

This was a randomised, investigator blinded, controlled effectiveness trial of supplementary feeding with either corn-soy blend or fortified spread. Food supplements were started at the same time as antiretroviral therapy and given for 14 weeks.

Our primary outcomes were changes in the BMI and the fat-free body mass after 14 weeks. Secondary outcomes were nutritional status, death, alive/nutritional status unknown, and lost to follow-up, quality of life, serum albumin concentration, haemoglobin concentration, CD4 count, HIV viral load, and adherence to antiretroviral therapy.

The sample size of 450 enabled detection of a difference in BMI and fat-free body mass of 0.5 kg between the two groups with 95% specificity and 80% power, allowing for 15% attrition.

Study procedures

On enrolment, we obtained demographic, clinical status, quality of life, and anthropometric measurements. Participants were seen at the clinic on four occasions: after two, six, 10, and 14 weeks. During each visit staff

assessed clinical status, administered questionnaires on quality of life and adherence to antiretroviral therapy, and measured body weight, bioelectrical impedance, and waist and mid-upper arm circumferences. They took blood samples at enrolment and at 14 weeks to measure serum albumin concentration, haemoglobin concentration, CD4 count, and HIV viral load.

Participants' diets on enrolment were assessed with a 24 hour dietary recall the day before enrolment. For each of the foods consumed they were asked whether the foods were consumed daily, weekly, or monthly. Dietary intakes were assessed with three different methods: the total number of different foods consumed, whether animal products were consumed or not, and a 12 point dietary diversity score that correlates with household food security.[7]

After the supplementary feeding period ended social scientists led open ended focus group discussions to explore compliance, acceptability, and sharing of the food supplements.

Study foods

Both supplementary foods provided the same level of energy, about 50% of the daily estimated average energy requirement.[8] See bmj.com. Neither provided amounts of micronutrients that significantly exceeded the estimated average requirement. Both groups of participants were advised to consider the food supplements as medical treatment and not to share it.

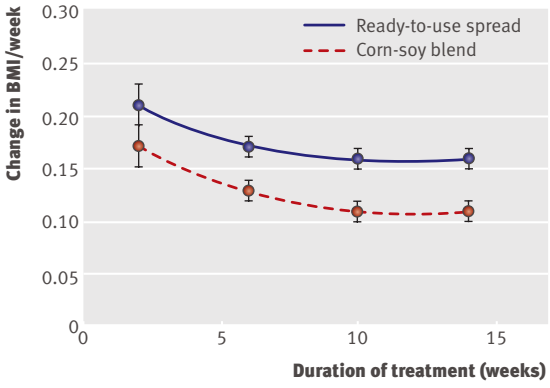
Statistical analysis

We calculated fat-free body mass using the equations developed for wasted adults with HIV.[9] BMI was measured at four points after enrolment (after two, six, 10, and 14 weeks). We calculated the rate of change in BMI during each of these intervals for each participant. To determine whether the rates of change in BMI during the 14 week feeding period differed between the two food groups, we compared the mean change in BMI during each interval for each food group. Weight gain during recovery from wasting follows an exponential decay pattern; when individuals are more wasted they regain weight faster, and as they approach a normal BMI, the rate of weight gain decreases.

We assessed the association between death and demographic, anthropometric, and immunological characteristics by Cox regression modeling. See bmj.com.

Outcomes in wasted adults with HIV at 14 weeks. Figures are means (SD) unless stated otherwise

	Fortified spread (n=245)	Corn-soy blend (n=246)	Difference (95% CI)
Gain in BMI	2.2 (1.9)	1.7 (1.7)	0.5 (0.2 to 0.8)
Gain in fat-free body mass (kg)	2.9 (3.2)	2.2 (3.0)	0.7 (0.2 to 1.2)
Gain in mid-upper arm circumference (cm)	2.2 (2.0)	1.6 (1.7)	0.6 (0.3 to 0.9)
Weight gain (kg)	5.6 (4.8)	4.3 (4.0)	1.3 (0.5 to 2.1)
BMI	19.0 (2.1)	18.4 (1.1)	0.6 (0.3 to 0.9)
Fat-free body mass (% of body composition)	89.0 (8.0)	91.0 (8.0)	2.0 (0.6 to 3.4)



Analysis of rate of BMI change for fortified spread *v* corn-soy blend. Data points represent mean (95% confidence interval)

RESULTS

We enrolled 491 participants (97%) of all eligible individuals during the study period. There were no significant differences in the demographic, anthropometric, or clinical characteristics between the two study groups at baseline. Seventeen (3.4%) participants were lost to follow-up, and 21 (4.3%) were known to be alive but missed their 14 week clinic visit and no anthropometric measurements were made. No adverse reactions to either food were reported. See bmj.com.

After 14 weeks of nutritional intervention and antiretroviral therapy, participants who received fortified spread had a greater increase in BMI, fat-free body mass, and mid-upper arm circumference than those who received corn-soy blend (table). Fat-free mass contributed to 2.9 kg (51.8%) of the 5.6 kg weight gain in the fortified spread group and 2.2 kg (51.2%) of the 4.3 kg weight gain in the corn-soy blend group. There were no significant differences in survival, HIV viral load strata, CD4 count, or quality of life between the groups.

Mortality was high in both groups: 131 (27%) participants died within the first 14 weeks. Male sex, not receiving co-trimoxazole prophylaxis, and a lower BMI, haemoglobin, or albumin on enrolment were independent risk factors of death at 14 weeks. See bmj.com. Self reported adherence to antiretroviral therapy was similar in both groups. Few participants reported missing a dose on the previous day or at least one dose in the previous week in either group.

The rate of change in BMI decreased during the supplementation period (figure), but the change in BMI was greater by a constant amount in the fortified spread group (0.045) compared with the corn-soy blend group throughout the entire supplementation period.

We examined outcomes in subgroups of participants stratified by the quality of their diet on enrolment and the type of supplementary feeding. Neither corn-soy blend nor fortified spread affected any dietary subgroup differently; diet on enrolment had no effect on outcome or on the benefit of either supplement. See bmj.com.

Ninety five participants attended the focus groups. Both study food supplements were universally highly appreciated. Nearly all participants said that sharing of

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

Many patients with HIV in sub-Saharan Africa are wasted and are commonly given supplementary food

The cost of supplementary feeding is considerable for HIV treatment programmes in sub-Saharan Africa

WHAT THIS STUDY ADDS

When wasted adults with HIV who are starting antiretroviral therapy are given a specialised ready-to-use lipid based fortified spread for 14 weeks they regain BMI more quickly than when given corn-soy flour

No differences were observed in mortality, CD4 count, viral load, HIV suppression, adherence to antiretroviral therapy, or quality of life between the food groups

both food supplements by dependents and family members was common, although corn-soy blend was more likely to be shared because it needed preparation by caregivers before consumption.

DISCUSSION

In wasted patients starting antiretroviral therapy, food supplementation with ready-to-use fortified spread resulted in a greater increase in BMI, fat-free body mass, and mid-upper arm circumference than corn-soy blend after 14 weeks. There were, however, no differences observed in mortality, CD4 count, HIV suppression, adherence to antiretroviral therapy, or quality of life between the groups. Weight gain with supplementary feeding was considerable, resulting in gains of 10% and 13% of initial body mass for corn-soy blend and fortified spread, respectively.

Limitations and major findings

Food consumption was not observed in either of the groups, therefore we do not know the degree of adherence with the dietary recommendations. As we did not have a control group of participants receiving no supplementary food, we do not know what the nutritional status would have been without supplementary feeding.

The analysis of the change in BMI with time indicates that during every interval in the 14 week study period, participants receiving fortified spread gained more BMI than those receiving corn-soy blend.

Fat-free mass contributed about the same fraction of the weight gain in each food group, suggesting that more of the fortified spread was consumed than corn-soy blend. Fortified spread might have promoted greater weight gain than corn-soy blend because of its higher energy density, thereby allowing adequate energy intake in patients with some degree of anorexia. The focus group discussions also indicated that fortified spread was shared less often; corn-soy blend is similar to components of the traditional diet, while fortified spread is regarded as a special supplement, a medicinal food. We found no evidence that those with a worse diet would benefit more from an energy dense food than those with a better diet.

Comparisons of clinical outcomes with other studies

Our findings are consistent with some previous observations of supplementary feeding with energy dense foods in people with HIV (Kaliwo G. Use of RUTF in Thyolo district. CTC workshop, 25 June 2004, Lilongwe, Malawi).[5 10] Our study is novel as it provides evidence that an energy dense food is associated with improved recovery from wasting, though this needs confirmation in other populations.

As the study was underpowered to detect differences in survival smaller than 5%, we might have failed to detect a small survival benefit. We observed a mortality rate of 27%. High early mortality rates are common in antiretroviral therapy programmes in sub-Saharan Africa. See bmj.com. The absence of co-trimoxazole prophylaxis was a strong risk factor for death. This suggests that invasive bacterial infections might have been an important cause of mortality, an observation found in other studies.[11-13] The high mortality rate in our study might also have been because of undiagnosed opportunistic infections, particularly tuberculosis.

Costs

The corn-soy blend provided in our study cost $5.40 (£3.58, €4.06) per patient per month, while fortified spread was three times as expensive at $16. The Malawian government obtains the first line antiretroviral therapy for $15 per patient per month. About a third of all adults starting antiretroviral therapy are wasted. Formal cost benefit analyses are required to determine whether supplementary feeding strategies are cost effective when compared with other elements of clinical care given to those with HIV.

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Competing interests: None declared.

Ethical approval: The study was approved by the college of medicine research and ethics committee, University of Malawi, the human studies committee of the Washington University School of Medicine, and the committee for research on human subjects at the University of the Witwatersrand.

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Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study

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ABSTRACT

Objective To evaluate the association between door-to-balloon time and mortality in hospital in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction to assess the incremental mortality benefit of reductions in door-to-balloon times of less than 90 minutes.

Design Prospective cohort study of patients enrolled in the American College of Cardiology National Cardiovascular Data Registry, 2005-6.

Setting Acute care hospitals.

Participants 43 801 patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention.

Main outcome measure Mortality in hospital.

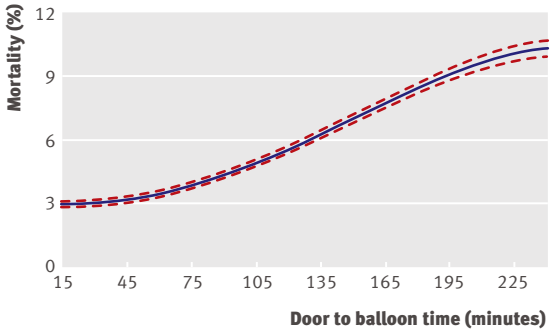
Results Median door-to-balloon time was 83 minutes (interquartile range 6-109, 57.9% treated within 90 minutes). Overall mortality in hospital was 4.6%. Multivariable logistic regression models with fractional polynomial models indicated that longer door-to-balloon times were associated with a higher adjusted risk of mortality in hospital in a continuous non-linear fashion (30 minutes=3.0%, 60 minutes=3.5%, 90 minutes=4.3%, 120 minutes=5.6%, 150 minutes=7.0%, 180 minutes =8.4%, P<0.001). A reduction in door-to-balloon time from 90 minutes to 60 minutes was associated with 0.8% lower mortality, and a reduction from 60 minutes to 30 minutes with a 0.5% lower mortality.

Conclusion Any delay in primary percutaneous coronary intervention after a patient arrives at hospital is associated with higher mortality in hospital in those admitted with ST elevation myocardial infarction. Time to treatment should be as short as possible, even in centres currently providing primary percutaneous coronary intervention within 90 minutes.

INTRODUCTION

Clinical guidelines recommend that hospitals providing primary percutaneous coronary intervention to patients with ST segment elevation myocardial infarction should treat patients within 90 minutes of contact.[1] Although most studies point to an independent association between longer time to treatment and higher mortality, the specific shape of the relation is unclear. While some studies indicate that any delay after admission is associated with higher mortality,[2-4] others suggest mortality is higher only after an initial delay in treatment of an hour or more.[5 6] In addition, it is unclear whether mortality is higher with successively longer times to treatment,[2-6] or if mortality eventually plateaus after two or more hours of delay.[7 8]

Current quality improvement initiatives seek to achieve a door-to-balloon time (that is, between arrival



Adjusted in hospital mortality as function of door-to-balloon time (modelled as fractional polynomial) with 95% confidence intervals

Estimated in hospital mortality (95% confidence interval) by door-to-balloon time in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction

Time (minutes)	Unadjusted	Adjusted*
15	2.6 (2.3 to 2.8)	2.9 (2.8 to 3.1)
30	2.8 (2.5 to 3.0)	3.0 (2.9 to 3.2)
45	3.1 (2.8 to 3.3)	3.2 (3.1 to 3.3)
60	3.4 (3.2 to 3.7)	3.5 (3.4 to 3.6)
75	3.9 (3.7 to 4.1)	3.8 (3.7 to 4.0)
90	4.4 (4.2 to 4.6)	4.3 (4.2 to 4.4)
105	5.0 (4.8 to 5.2)	4.9 (4.8 to 5.0)
120	5.6 (5.4 to 6.0)	5.6 (5.4 to 5.7)
135	6.3 (6.0 to 6.7)	6.3 (6.1 to 6.4)
150	7.0 (6.6 to 7.5)	7.0 (6.8 to 7.2)
165	7.7 (7.2 to 8.3)	7.7 (7.5 to 8.0)
180	8.4 (7.7 to 9.1)	8.4 (8.2 to 8.7)
195	8.9 (8.2 to 9.8)	9.1 (8.8 to 9.4)
210	9.4 (8.5 to 10.3)	9.7 (9.3 to 10.0)
225	9.7 (8.7 to 10.8)	10.1 (9.7 to 10.4)
240	9.8 (8.7 to 11.0)	10.3 (10.0 to 10.7)

*Adjusted for sex, age, race, findings on presentation, medical history, procedural characteristics, angiographic findings, and hospital factors.

at hospital and treatment) of 90 minutes or less among 75% or more of patients undergoing primary percutaneous coronary intervention.[9] Several hospitals have shown that it is possible to achieve median door-to-balloon times approaching 60 minutes.[10] Relatively little data exist regarding the incremental benefit of further reductions beyond 90 minutes.

We analysed data from a large national US database containing medical records of patients undergoing percutaneous coronary intervention. We hypothesised that any increase in door-to-balloon time would be associated with increased mortality and that this mortality risk would persist irrespective of the length of the delay in treatment.

METHODS

National Cardiovascular Data Registry

The registry is sponsored by the American College of Cardiology and contains details of patients undergoing cardiac catheterisation at more than 600 participating centres in the United States. Sites were encouraged to prospectively collect detailed clinical information from all patients undergoing cardiac catheterisation.

Study sample

We limited our analysis to patients who, in 2005-6, presented to a participating centre within 12 hours of symptom onset with laboratory and electrocardiographic evidence of ST elevation myocardial infarction and subsequently underwent primary percutaneous coronary intervention (n=64 676). We excluded patients who were transferred from other hospitals (n=17 992), or who first received fibrinolytic therapy (n=3313) and patients under 18 years or over 99 years (n=9). Finally, to minimise data coding errors, we excluded patients treated at hospitals that reported fewer than five primary percutaneous coronary interventions (n=29), leaving 45 687 patients eligible for analysis.

Door-to-balloon time

Door-to-balloon time was defined as the time in minutes between a patient's arrival at the hospital and the first balloon inflation or device deployment as documented in the patient's medical record.

Of the 45 687 patients eligible for analysis, we excluded patients for whom door-to-balloon time was missing (n=503) or with a door-to-balloon time <15 minutes (n=971) or >6 hours (n=915) to avoid potentially incorrectly coded time or primary strategy. The final study sample consisted of 43 801 patients.

Statistical analysis

We determined the mean, median, and distribution of door-to-balloon times. We compared differences in patients' demographic and clinical characteristics. Logistic regression analysis with fractional polynomial modelling (a combination of linear and non-linear transformations of door-to-balloon time) determined the specific shape of the unadjusted association between door-to-balloon time and mortality in hospital. We repeated analyses adjusting for patients' characteristics associated with mortality derived from the registry mortality model.[11] Variables included sex, race, age, findings at presentation, medical history, procedural characteristics, angiographic findings, and hospital characteristics.

RESULTS

The median door-to-balloon time in the study cohort was 83 minutes (interquartile range 62-109 minutes), with 25 359 patients (57.9%) treated within 90 minutes of admission. A greater proportion of patients who had longer door-to-balloon times were women, non-white, and older than patients with shorter door-to-balloon times. Patients with longer door-to-balloon times had more comorbidities than patients with shorter door-to-balloon times, including a higher prevalence of previous myocardial infarction, heart failure, diabetes, hypertension, peripheral vascular disease, and previous revascularisation. Patients with shorter door-to-balloon times had a lower incidence of cardiogenic shock and stenoses of the left main and left anterior descending arteries, and a greater proportion had Society of Cardiac Angiography and Intervention IV lesions. See full details on bmj.com.

Mortality in the study cohort was 4.6% (1999/43 801) overall. Patients who died in hospital had a 14 minute longer median door-to-balloon time than patients who

survived (96 *v* 82 minutes, P<0.001). Patients with longer door-to-balloon time had higher crude mortality across four door-to-balloon time groups (<60 minutes=3.2% (323/9971), 60-89 minutes=3.7% (568/15 388), 90-119 minutes=4.6% (473/10 208), ≥120 minutes =7.7% (635/8234), P<0.001 for trend).

Logistic regression analysis with a third degree fractional polynomial best modelled the unadjusted association of door-to-balloon time with mortality, showing an increased risk of mortality associated with any delay in door-to-balloon time. Estimated unadjusted mortality ranged from 2.8% for patients with door-to-balloon times of 30 minutes to 9.8% for patients with door-to-balloon times of 240 minutes (table).

Longer door-to-balloon times continued to be associated with increased mortality after multivariable adjustment (figure), with any delay in door-to-balloon time associated with an increased mortality risk. Estimated adjusted mortality ranged from 3.0% for patients with door-to-balloon time of 30 minutes to 10.3% for patients with door-to-balloon times of 240 minutes (table).

DISCUSSION

Any delay in door-to-balloon time for patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention is associated with higher mortality, even among patients treated within 90 minutes of admission. The mortality risk with door-to-balloon time persists irrespective of the length of the treatment delay.

Comparison with other studies

Our analysis improves on previous studies that modelled time to treatment as a categorical[5-7 12-17] or continuous linear variable.[2 4] Use of categorical variables might result in a loss of statistical power, which could explain why certain studies report no increased risk associated with delayed time to treatment.[12-15 18] By modelling time to treatment as a linear continuous variable, previous analyses assumed each additional delay in treatment was associated with the same additional increased risk in mortality.[19] By using fractional polynomial regression, we made no assumptions regarding the shape of the association between time to treatment and mortality.

While some studies found that increased mortality associated with delays was present solely within the first few hours of presentation and then plateaued,[16 18] others had suggested the reverse—a risk that was initially unchanged and increased only after a few hours of delay.[5 6] Our study suggests that both reports might be correct as the mortality risk associated with delay was present immediately after admission and persisted for several hours. Differences in study findings largely reflect the manner in which different studies have modelled time to treatment rather than contradictory findings regarding the relation between time and outcomes.

Pathophysiology of delayed time to treatment

Experimental models have shown that the continuous, progressive "wave front of necrosis" largely depends on the duration of ischaemia.[20] Patients with longer door-to-balloon times will experience longer periods of vessel occlusion, resulting in more ischaemia and greater necrosis than patients with shorter times to treatment.[21] Although there might be benefits to reperfusion therapy performed after long delays,[22] our data suggest that these benefits do not offset the underlying myocardial necrosis and attendant processes resulting from longer delays in time to treatment.[23]

Implications for practice

Our data show that reducing average door-to-balloon times from 90 minutes to 60 minutes might reduce in hospital mortality by as much as 0.8% (from 4.3% to 3.5%). A further 30 minute reduction in door-to-balloon to an average of 30 minutes offers the potential of an additional 0.5% reduction (from 3.5% to 3.0%). These data support calls for an "as soon as possible" standard for patients undergoing primary percutaneous coronary intervention.

Study limitations

Our study has several limitations. Firstly, we were unable to assess the association of time from the onset of symptoms to arrival at hospital and mortality or the association of total ischaemic time and mortality. We attempted to limit this effect by conducting a secondary analysis restricted to patients who presented within six hours of symptom onset and found our results were similar (see bmj.com). Secondly, we assessed the outcome of in hospital mortality and cannot comment on the association of door-to-balloon time and mortality at later end points. Previous studies have reported that the association of door-to-balloon time and mortality is comparable whether assessed during hospital admission, at 30 days, or at one year. Finally, as our analysis was based on observational data our findings might be attributable to biases introduced by unmeasured factors.

Conclusion

Door-to-balloon time is associated with mortality in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction. Contrary to previous studies, we found that this risk was present on admission and was not attenuated with the passage of time. Our findings suggest a benefit from reducing door-to-balloon time for all patients undergoing primary percutaneous coronary intervention, including those currently treated within 90 minutes of hospital admission.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical guidelines recommend that hospitals providing primary percutaneous coronary intervention to patients with ST segment elevation myocardial infarction treat within 90 minutes of contact with the medical system or admission to hospital

The specific shape of the relation between mortality risk and time to treatment, and the incremental benefit of reductions in door-to-balloon times beyond 90 minutes, is unclear

WHAT THIS STUDY ADDS

Any delay in door-to-balloon time for patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention is associated with higher mortality, even among patients treated within 90 minutes of admission

Reducing door-to-balloon time to the greatest extent possible for all patients, including those currently treated within 90 minutes of admission, might reduce mortality

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Prevalence of disease related prion protein in anonymous tonsil specimens in Britain: cross sectional opportunistic survey

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STUDY QUESTION What is the prevalence of disease related prion protein (PrP^{CJD}) in the population of Britain?

SUMMARY ANSWER We found no evidence for PrP^{CJD} in 63 007 tonsils, of which nearly 13 000 were in the birth cohorts from which most cases of variant Creutzfeldt-Jakob disease (vCJD) have arisen (1961-85). This gives a prevalence estimate of 0 to 289 per million tonsils, which is lower than, but still consistent with, a previous estimate derived from a survey of appendixes.

Participants, setting, and design

Anonymised tonsil pairs removed at elective tonsillectomy throughout England and Scotland were tested. Patients or their carers had been given a leaflet explaining the study, and an explicit paragraph and tick box to exercise a right to opt out of inclusion in the survey were included in the pre-tonsillectomy consent forms.

Primary outcome(s)

Presence of PrP^{CJD} was determined by using two different serological assays. Any sample that showed reactivity in either assay was investigated further by immunohistochemistry and immunoblotting.

Main results and the role of chance

Of the 63 007 samples tested, none was unequivocally reactive in both screening assays. Only two samples were reactive in one assay and equivocal in the other, and nine samples were equivocally reactive in both. Two hundred and seventy six samples were initially reactive in one or other assay. None of the samples (including all the 276 assay reactives) that were investigated by immunohistochemistry or immunoblotting was positive for the presence of PrP^{CJD}.

The observed prevalence of PrP^{CJD} in tonsils from the 1961-95 birth cohort was 0/32 661 with a 95% confidence interval of 0 to 113 per million. In the 1961-85 cohort, the prevalence was zero with a 95% confidence interval of 0 to 289 per million. This is lower than, but still consistent with, a previous survey of appendixes that showed a prevalence of 267 per million with a 95% confidence interval of 55 to 779 per million.

Bias, confounding, and other reasons for caution

Although we have confidence in these results, the following caveats should be borne in mind. Firstly, tonsil tissues from people exposed to bovine spongiform encephalopathy (BSE) who were healthy and incubating vCJD were not available to directly prove that PrP^{CJD} is detectable in them. The assays we used, however, were shown to be sufficiently sensitive to detect PrP^{CJD} at levels down to 1/1000 of that in tonsil tissue from vCJD patients. Secondly, tonsillectomies are more common in the younger population who would not have been exposed to disease related PrP^{CJD}, as cattle affected by BSE have been removed from the food chain. We were able to collect and test 12 753 tonsils from the birth cohort in which most vCJD cases have arisen (1961-85) and 19 908 from the 1986-95 cohort that would also have been exposed to BSE through infected meat or meat products.

Generalisability to other populations

The population of Britain was most heavily exposed to BSE, but other countries, such as France and Ireland, have seen appreciable numbers of cases of vCJD. We expect that our estimate of the prevalence of PrP^{CJD} will be especially pertinent for these countries.

Study funding/potential competing interests

The study was funded by the Department of Health; the work was carried out independently of the funder.

PREVALENCE OF DISEASE RELATED PRION PROTEIN (P^{CJD}) IN BRITAIN IN THREE BIRTH COHORTS AND OVERALL (POSITIVE/TOTAL; RATE PER MILLION WITH 95% CONFIDENCE INTERVALS*)

	Current national tissue survey (2004–September 2008)	Earlier (1995-9) national tissue survey	
Birth cohort	Tonsils	Appendixes	Tonsils
1961-85	0/12 753; 0 (0-289)	3/10 278; 292 (60-853)	0/694
1986-90	0/9564; 0 (0-386)	0/396	0/119
1991-5	0/10 344; 0 (0-357)	Not applicable	0/106
Total†	0/63 007; 0 (0-59)	3/11 247; 267 (55-779)	0/1427; 0 (0-2582)

*Only calculated when denominator exceeds 1000
†Includes samples tested from other birth cohorts