

identified, remains uncertain; but evidence exists that all play a part in memory, appetite, the control of movement, and, especially, the modulation of pain.¹ With respect to the last of these, the sites of cannabinoid action in the central nervous system are confined to specific areas, most of which—the dorsal horn of the spinal cord, for example^{2–3}—are involved in processing pain signals. Clear parallels exist between cannabinoid and opioid receptors, and evidence is accumulating that the two systems sometimes interact,⁴ and may operate synergistically. One unproved but intriguing idea is that endocannabinoids may set the “analgesic tone” of the body, with the level of their production acting as a kind of pain thermostat.

The perception of pain is controlled by neurotransmitter systems within the central nervous system, but peripheral tissues also have mechanisms for relieving and preventing pain. Cannabinoids may therefore have two distinct roles in relation to pain. The evidence comes from animal experiments showing that cannabinoids lower the response of pain neurones in the spinal cord and also in parts of the thalamus in the brain. The possibility that cannabinoid receptor subtypes act synergistically hints at a potentially valuable strategy: the development of a new class of analgesic drug comprising a mixture of synthetic CB₁ and CB₂ agonists. Alternatively, devising agents to slow the breakdown of natural cannabinoids might potentiate their analgesic effects.⁵

The brain has many more CB₁ than opioid receptors, and interest in the therapeutic potential of cannabinoids has prompted the development of several synthetic variants, of which dronabinol is one.¹ Many of these compounds bind to both CB₁ and CB₂ receptors, but differences between the two suggest that it should be possible to design drugs that would attach to only one of them. This might offer a means of producing more selective biological actions, including analgesia without some of the psychotropic effects that might disturb people whose wish was to be pain-free but not “high.”

A review by the US Institute of Medicine has commented on how little we know about cannabinoids in comparison with opiates.² A comparison between the history of research into the two groups, the review added, “suggests good reason for optimism about the future of cannabinoid drug development.”

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Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery

Moira McKendry, Helen McGloin, Debbie Saberi, Libby Caudwell, Anthony R Brady, Mervyn Singer

Abstract

Objective To assess whether a nurse led, flow monitored protocol for optimising circulatory status in patients after cardiac surgery reduces complications and shortens stay in intensive care and hospital.

Design Randomised controlled trial.

Setting Intensive care unit and cardiothoracic unit of a university teaching hospital.

Participants 174 patients who had cardiac surgery between April 2000 and January 2003.

Interventions Patients were allocated to conventional haemodynamic management or to an algorithm guided by oesophageal Doppler flowmetry to maintain a stroke index above 35 ml/m².

Results 26 control patients had postoperative complications (two deaths) compared with 17 (four deaths) protocol patients (P = 0.08). Duration of hospital stay in the protocol group was significantly reduced from a median of nine (interquartile range 7-12) days to seven (7-10 days; P = 0.02). The mean duration of hospital stay was reduced from 13.9 to

11.4 days, a saving in hospital bed days of 18% (95% confidence interval – 12% to 47%). Usage of intensive care beds was reduced by 23% (– 8% to 59%).

Conclusions A nurse delivered protocol for optimising circulatory status in the early postoperative period after cardiac surgery may significantly shorten hospital stay.

Introduction

Hypovolaemia and tissue hypoperfusion can pass undetected during and after major surgery.¹ These are often not clinically apparent for several days, and may lead to increased morbidity and mortality.

Several perioperative studies have used invasive (pulmonary artery catheterisation) or minimally invasive (oesophageal Doppler flowmetry) monitoring technologies to optimise circulatory variables,² and

Bloomsbury
Institute of
Intensive Care
Medicine,
Department of
Medicine and
Wolfson Institute
of Biomedical
Research, University
College London,
Middlesex Hospital,
London W1T 3AA

Moira McKendry
research sister
Helen McGloin
research sister
Debbie Saberi
research sister
Libby Caudwell
research sister
Mervyn Singer
professor of intensive
care

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have shown major improvements in postoperative complications and stay in intensive care or hospital. Others, however, have found no improvement in outcomes.³ To our knowledge, only one randomised study has specifically investigated optimisation of circulatory status after cardiac surgery,⁴ and this reported a reduction in median duration of hospital stay.

We previously reported that a low stroke volume index ($<35 \text{ ml/m}^2$) and a high heart rate on admission to intensive care after cardiac surgery and at four hours were the best prognostic factors for the development of subsequent complications.⁵ We therefore studied the optimisation of circulatory status in patients in the first four hours, randomising them to receive treatment guided by oesophageal Doppler flowmetry to achieve a stroke volume index above 35 ml/m^2 . This trial differs from the previous study in two major respects.⁴ Firstly, cardiac output was monitored using minimally invasive technology and, secondly, nurses conducted the study using a protocol driven approach.

Participants and methods

Participants were undergoing cardiopulmonary bypass surgery. We excluded patients undergoing off-pump surgery, aged under 18 years, or with relative contraindications to the use of the oesophageal Doppler probe, such as oesophageal disease. Patients were also excluded postoperatively if on admission to intensive care there was excessive bleeding, unstable arrhythmias, a need for intra-aortic balloon counterpulsation, or inotrope requirements $\geq 10 \mu\text{g/kg/min}$ of dopamine or dobutamine or $\geq 0.16 \mu\text{g/kg/min}$ of adrenaline (epinephrine) or noradrenaline (norepinephrine).

For the oesophageal Doppler technique a 6 mm probe was placed into the lower oesophagus through the mouth or nose. The probe is directed to detect midstream blood flow in the descending thoracic aorta, with the aid of an online monitor and an integral loudspeaker.

Objectives and intervention

Our primary objective was to compare the lengths of stay in intensive care and hospital after cardiac surgery between protocol and control groups, and secondary objective to compare postoperative complications between the two groups.

The control group received standard postoperative care determined by the intensive care and cardiac surgical teams. This, as in most UK centres, uses markers of tissue perfusion such as urine output and arterial base deficit. Monitoring of cardiac output could be included if considered clinically indicated. Within 10 minutes of admission to the intensive care unit and at four hours postoperatively, the study nurse took readings from these patients with an oesophageal Doppler probe. Doctors and nurses not involved with the study were not allowed sight of these readings. If patients in either group were ready for extubation before four hours, a Doppler recording was made before removal of the endotracheal tube.

The oesophageal Doppler probe was also inserted within 10 minutes of arrival of the protocol patients on the intensive care unit. The algorithm in figure 1 was followed to increase the stroke volume index to ≥ 35

ml/m^2 or greater using repeated colloid challenges, with nitrates and inotropes given as required. This management was directed by the study nurse, with indications for referral to medical staff.

Recordings of standard haemodynamic variables and intravenous fluid and drug requirements were made manually over the first four hours. Follow up data were collected on days 1, 2, and 5 postoperatively, including complications, time to extubation, and length of stay in intensive care and hospital. If the patient was medically fit for hospital discharge but this was delayed for social or logistical reasons, a note was made. Both patients and staff on the general wards to which patients were sent after intensive care were unaware of the group assignment.

Statistical analysis

Patients were randomised on arrival at intensive care. We calculated a sample size of 170 patients (85 in each group), and tested for differences in postoperative measurements and complications between treatment groups (see bmj.com).

Results

Overall, 179 patients were recruited between April 2000 and January 2003 (see bmj.com). After exclusions, there were 89 patients in the protocol group and 85 in the control group. The groups were well matched for age, sex, weight, Parsonnet cardiac risk score, and

Intensive Care
National Audit and
Research Centre,
BMA House,
London WC1H 9JR
Anthony R Brady
statistician

Correspondence to:
M Singer
m.singer@ucl.ac.uk

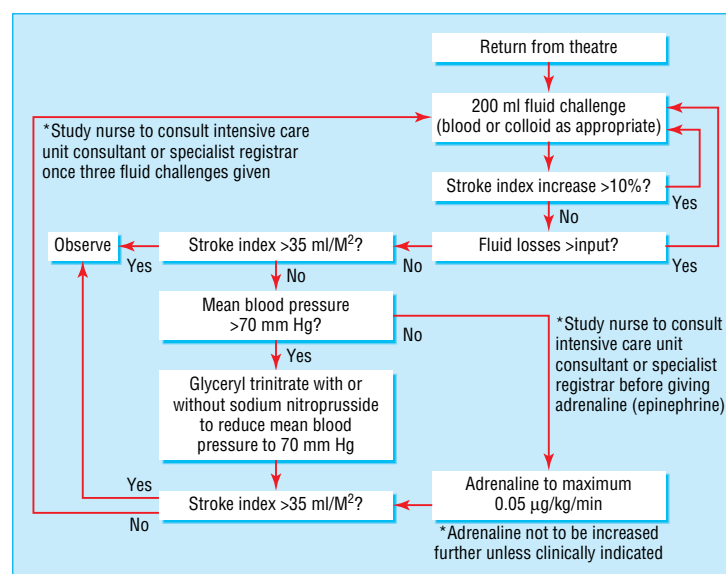


Fig 1 Treatment algorithm to optimise circulatory status in patients after cardiac surgery

Management of patients in four hours after cardiac surgery. Values are means (standard deviations)

Measure	Control group (n=85)	Protocol group (n=89)	P value
Fluid requirement:			
Colloid (ml)	1042 (620)	1667 (464)	<0.001
Crystalloid (ml)	328 (99)	353 (95)	0.09
Change in measure:			
Stroke volume (ml)	-10.2 (18.4)	1.5 (18.9)	<0.001
Cardiac output (l/min)	-0.46 (1.68)	0.45 (1.98)	0.001
Corrected flow volume (ms)	-32.5 (59.7)	-6.2 (67.5)	0.007
Peak velocity (cm/s)	-2.7 (16.6)	2.6 (14.4)	0.03
Arterial base excess (mmol/l)	-0.73 (1.60)	-0.54 (2.19)	0.50

type of surgery.⁶ The median first 24 hour acute physiological and chronic health evaluation II score was similar in both groups (10 protocol, 11 control).

The table shows the haemodynamic data and fluid requirements over the initial four hour postoperative period. Although stroke volume index, cardiac index, and use of colloid were well matched at baseline (within 10 minutes of admission), they were significantly greater in the protocol group at four hours; use of inotropes was similar between the two groups. Colloid was given to all but one of the control patients. None of the control patients had pulmonary artery catheters in situ or had Doppler probes placed because of perceived clinical need. Inotropes were not instituted as per protocol to increase stroke volume indices to 35 ml/m² or greater owing to the short duration of the study and the frequent need for repeated fluid challenges in the study period. At four hours, 35 (39%) protocol patients and 48 (56%) control patients had values below 35 ml/m².

In the protocol group, the mean number of days in intensive care, although not statistically significant, was reduced from 3.2 to 2.5 (23% reduction, 95% confidence interval -8% to 59%; fig 2). The mean duration of hospital stay in this group was reduced from 13.9 to 11.4 days (18% reduction, -12% to 47%), with a significant reduction in median duration of stay from nine to seven days ($P = 0.02$).

Four deaths occurred in the protocol group and two in the control group, the causes of which were not considered directly attributable to early postoperative care. Comparisons of length of stay in survivors only were similar to those for all patients. The protocol group showed a trend towards fewer major postoperative complications and deaths than the control group (see [bmj.com](#)).

Discussion

A nurse delivered protocol to optimise circulatory status of patients early after cardiac surgery, using oesophageal Doppler flowmetry and targeted at improving stroke volume, reduced the length of hospital stay. This protocol was also associated with a trend towards fewer complications and reduced stay in intensive care.

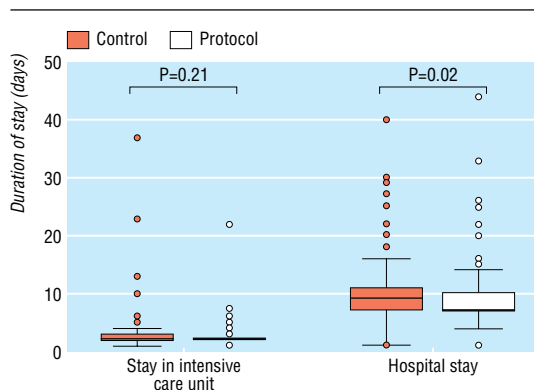


Fig 2 Duration of stay in intensive care and hospital in patients receiving strategy to optimise circulatory status after cardiac surgery (protocol) or conventional management (control)

What is already known on this topic

After cardiac surgery many patients have complications that prolong hospital stay

Perioperative tissue hypoxia is the postulated trigger for many of these complications

What this study adds

Optimisation of intravascular volume in the first four hours postoperatively reduces complications and bed usage

Nurses could deliver the protocol using a minimally invasive device that monitors stroke volume and responses to interventions

Tissue hypoperfusion is common in patients perioperatively and is associated with high postoperative morbidity and mortality. Non-cardiac complications have been found to be associated with more adverse outcomes.⁷ As in our study, these were independent of Parsonnet score and bypass time.

Optimisation of circulatory status perioperatively was a concept first promulgated by Shoemaker.⁸ Comparable results from other groups using a similar goal directed approach lends further support to the importance of avoiding a tissue oxygen debt perioperatively.⁹⁻¹¹ In large Canadian and US studies, however, placement of a pulmonary artery catheter without targeting predefined haemodynamic end points produced no difference in postoperative outcomes.^{3 12} We believe our results are generalisable to countries where monitoring of cardiac output is performed more often during cardiac surgery than in the United Kingdom, and emphasise the need to obtain maximum utility from a monitoring technique by titrating therapy.

The necessity for treatment to be directed by invasive monitoring (pulmonary artery catheterisation) has been challenged by several groups that used oesophageal Doppler flowmetry to maximise intraoperative stroke volume by repeated fluid challenges.¹³⁻¹⁶ These studies showed important (30-40%) reductions in length of hospital stay after cardiac, orthopaedic, or abdominal surgery. The lesser reduction in mean length of hospital stay (18%) achieved by us is comparable to that reported by Polonen,⁴ showing that optimisation of circulatory status should ideally begin at the start of, if not before, a major operation.

Our study shows that nurses can safely insert and align the oesophageal Doppler probe to detect descending aortic blood flow within a few minutes. Although staff could not be blinded to the randomisation schedule, the subsequent management of patients after the first four hours was identical and they were not made aware of the Doppler results.

The intention to use inotropes if fluid loading failed to achieve a target stroke index was not met, mainly because of time constraints but in part to the reticence of the nurses. Our study should thus be viewed as a trial of immediate optimisation of fluid status in the postoperative period.

Weaknesses of our trial were that it was of relatively small size and conducted in only one centre. A larger

multicentre trial is needed to confirm the generalisability of our findings and the effect on mean rather than median length of hospital stay, which is more relevant to costs.

In conclusion, improvements in postoperative outcomes in patients after cardiac surgery may be achieved by early intervention targeted at optimising the stroke volume. A nurse delivered, protocol driven approach has the potential for widespread application as it is not routinely feasible for a clinician to be constantly at the bedside.

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Contributors: See bmj.com

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Ethical approval: Ethics committee University College London Hospitals NHS Trust.

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Change in suicide rates for patients with schizophrenia in Denmark, 1981-97: nested case-control study

Merete Nordentoft, Thomas Munk Laursen, Esben Agerbo, Ping Qin, Eyd Hansen Høyer, Preben Bo Mortensen

Abstract

Objective To study the change in risk of suicide among patients with schizophrenia and related disorders.

Design Nested case-control design with linked data.

Setting Four longitudinal Danish registers.

Participants 18 744 people aged up to 75 years who committed suicide in 1981-97 individually matched with 20 controls.

Results Over the time studied the reduction in suicide rate among patients with schizophrenia and schizophrenia spectrum disorder was similar to that seen in the general population (incidence rate ratio 1.00, 95% confidence interval 0.98 to 1.03). The reduction among patients with other psychosis in the schizophrenia spectrum was faster than the reduction seen in the general population. Among people admitted to hospital with schizophrenia the risk of suicide was highest in the first year after first admission, and the excess risk was largest in the

younger age groups—that is, the risk decreased per year for every additional year of age.

Conclusion The suicide rate among patients with a diagnosis of schizophrenia and related disorders has fallen. This may be due to better psychiatric treatment, reduced access to means of suicide, or improvements in treatment after suicide attempts.

Introduction

In 1980, the suicide rate in Denmark peaked and reached a level that was among the highest in the world, with 34 suicides per 100 000 inhabitants. After 1980 the number of suicides decreased each year, and in 1997 the rate was 15 per 100 000 inhabitants, a 56% reduction.

In Denmark, about half of the people who commit suicide have previously been admitted to psychiatric

Bispebjerg Hospital,
Department of
Psychiatry,
Bispebjerg Bakke
23, 2400
Copenhagen NV,
Denmark
Merete Nordentoft
associate professor

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