

Catecholamines for shock: the quest for high-quality evidence

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Catecholamines are a fundamental component of the defence of systemic perfusion in critically ill patients. Noradrenaline, adrenaline and dopamine have a long-standing place in clinical practice and are used primarily for the treatment of shock states, specifically to increase mean arterial pressure and cardiac output through sympathetically mediated cardiovascular effects. Despite this role, few high-quality studies exist that define the influence of these drugs in shock states on patient-centred outcomes, such as mortality, resolution of shock, end-organ failure, and duration of intensive care or hospital admission.

A comprehensive body of basic science research has been published that defines the biological actions of catecholamines in maintaining cardiovascular homeostasis under physiological and pathological conditions.¹⁻³ These studies, most of which have been conducted under laboratory conditions or in animals, provide important insights into the molecular biology and pharmacology of complex neurohumoral systems. However, despite the exponential increase in scientific knowledge about these systems, the translation of basic science research into clinical practice remains limited. This is reflected by the static descriptions of the pharmacodynamic effects of these drugs in standard texts and review articles.

This article will review the reasons for the limited translation of basic science research into clinical practice, summarise the state of patient-centred catecholamine research, outline a research strategy to define appropriate outcomes, and present the results of emerging research in this area.

The barrier between science and practice

Unlike pharmacological therapies for common cardiovascular conditions, such as hypertension and acute coronary syndromes, the treatments for hypotension and shock have changed little over the past 30 years. This is remarkable, given the prominence of acute medicine within academic and regional hospitals, where the vast majority of patients with shock are treated.

The principles of the treatment of shock are directed at a broad-based resuscitative strategy of oxygenation, restoration of normovolaemia and augmentation of blood pressure. These principles of "rescue therapy" have been widely adopted by clinicians, and are considered an effective and appropriate approach. The widespread adoption of resuscitation

ABSTRACT

Despite the established role of catecholamines for the treatment of circulatory shock in intensive care medicine, these drugs have been subjected to few randomised controlled trials with high methodological quality and patient-centred outcomes. The literature has been dominated by low-quality, case-control studies of the effects of synthetic catecholamines on surrogate haemodynamic end-points. A recent Cochrane systematic review of the effects of vasopressors on mortality from circulatory shock identified seven randomised controlled trials, none of which demonstrated any conclusive evidence of benefit of one inotrope/vasopressor over another. The review confirmed the persisting low methodological quality of these studies.

Three higher-quality studies of catecholamines (noradrenaline, adrenaline, dopamine and vasopressin) have been completed, the results of which will provide some evidence of efficacy of catecholamines on mortality and resolution of shock. These studies may provide the basis for designing and conducting a large-scale, pragmatic, randomised controlled trial to analyse the effects of these commonly used drugs on patient-centred outcomes, such as mortality, resolution of organ failure and hospital length of stay. The results of such a study would be particularly important in geographical regions where access to inotropes/vasopressors other than adrenaline remains restricted.

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protocols, particularly in trauma, has been associated with some evidence of parallel improvements in patient survival.

The selection and use of catecholamines within these pragmatic resuscitative strategies incorporates basic physiological and pharmacological principles (often faithfully propagated in text books and review articles), clinician preferences and institution-based protocols. Adrenaline, noradrenaline and dopamine have been used for over 30 years, and a substantive body of clinical experience has developed in the absence of high-quality, randomised controlled trials. Given the accepted use and ubiquitous

availability of these drugs, there appears to be little imperative for their study by clinicians and funding agencies. Furthermore, given that they are off-patent and inexpensive, there is little financial incentive on the part of industry. However, without high-quality data, it is impossible to quantify the attributable benefit of the selection and use of catecholamines within a complex resuscitative strategy.

Most of the published literature on catecholamines has been influenced and dominated by the synthetic drugs, notably dopamine, dobutamine and dopexamine. The use of these drugs, particularly dobutamine, was promoted within a loosely defined strategy of "supranormal" oxygenation, described in 1988.⁴ This involved the augmentation of oxygen delivery with dobutamine and red cell transfusion to minimise pathological "oxygen supply dependency". The physiological basis of this strategy is limited and focuses primarily on convective oxygen transport, which has little to do with biological cellular respiration and substrate utilisation. Ensuing publications comprised case-control series characterised by non-physiological surrogate end-points and substantial involvement of sponsoring industry. Following almost a decade of such studies, a meta-analysis (which included one randomised controlled trial⁵) concluded that there was no evidence that a strategy of "supranormal" oxygen optimisation affected mortality.⁶

Other studies on synthetic or non-synthetic catecholamines, used either as single agents or in combination with other drugs, emerged during this period. Most of these studies, usually conducted in patients with severe sepsis, employed combinations of noradrenaline and dobutamine,^{7,8} largely reflecting European and North American practice, although a few studies emerged of adrenaline^{9,10} (the most commonly used and often only available catecholamine in many parts of the developing world). These studies were invariably single-centre and underpowered, and used wide dose ranges with surrogate outcome measures. Methodological indices of quality, such as allocation concealment, intention-to-treat analysis, high completion and follow-up rates, and patient-centred outcomes were invariably absent. Few of these studies received funding from major granting bodies. Not surprisingly, the strength, generalisability and applicability of their results were limited.

Fewer studies emerged in cardiogenic shock, with most of the published reviews using data extrapolated from chronic heart failure trials that had little generalisability or applicability to acute shock states.

Therefore, despite the expansion of the body of basic science literature on catecholamine pharmacobiology, no adequately powered studies with high-quality methodology have been published on any of the catecholamines. The clinical evidence that does exist is dominated by studies with low-quality methodology and publication bias, limiting their

value as a basis for evidence-based guidelines. This is exemplified in the Surviving Sepsis Guidelines published in 2005,¹¹ where no Grade A recommendations could be made on the selection or use of a particular catecholamine.¹²

High-quality evidence for catecholamines in humans

The state of human catecholamine research in intensive care medicine was highlighted in a systematic review of vasopressors for shock published by the Cochrane Collaboration in 2004.¹³ This review aimed to assess whether particular "vasopressors" (defined as noradrenaline, adrenaline, dopamine, dobutamine and vasopressin) reduced overall mortality in critically ill patients with circulatory shock.

The investigators focused on studies with high-quality methodology and patient-centred outcomes: mortality (the main outcome measure), pre-defined indices of morbidity (length of hospital and ICU stay, resolution of shock and other organ failures), and measures of health-related quality of life. No language restrictions were applied. Blinded and unblinded randomised controlled trials comparing various vasopressors (alone, or in combination, with placebo or with intravenous fluids) for any kind of circulatory shock were included. Crossover trials and paediatric and animal studies were excluded.

Assessment of methodological quality included indices of validity (allocation concealment, blinded outcome assessment and intention-to-treat analysis) and quantitative data synthesis (ie, negligible clinical heterogeneity, and determination of combined relative risk).

Results of the literature search are summarised in Figure 1. Eight studies met the inclusion criteria, of which seven were conducted in patients with severe sepsis or septic shock. A single-centre study compared terlipressin with noradrenaline for refractory hypotension after anaesthesia for carotid endarterectomy in 20 patients. The remaining seven studies, six of which were conducted in single centres, enrolled a total of 172 patients (mean, 24 patients per study). Overall, the quality of methodology was unsatisfactory: only two studies analysed data by intention-to-treat, two reported allocation concealment, and two reported blinded outcome assessments. No single study attained a high level of methodological quality. The most commonly used vasopressor was noradrenaline (usually in combination with dobutamine), compared with adrenaline or dopamine. No study demonstrated any reduction in mortality with any vasopressor. The studies are summarised in Table 1.

This systematic review is a compelling demonstration of the lack of quality evidence to inform clinicians about the selection and use of vasopressors in shock. No drug or

Figure 1. Results of a literature search for studies on vasopressors in shock¹³

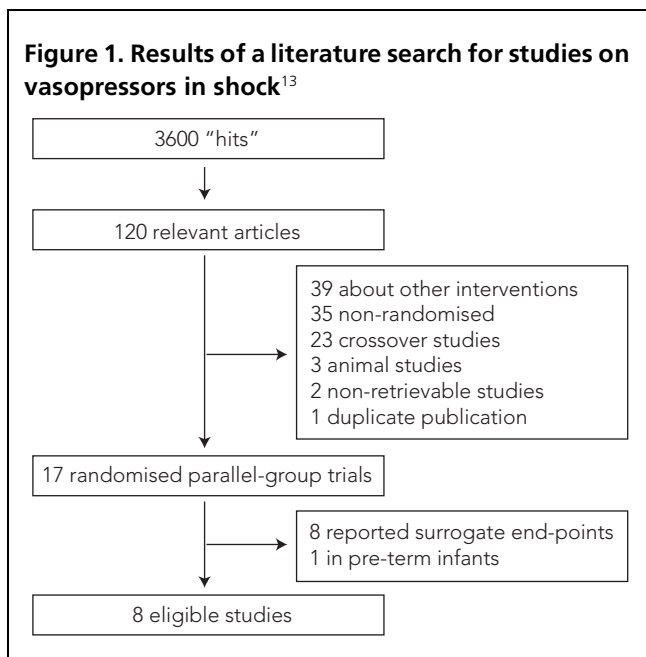


Table 1. Cumulative relative risk (RR) of death for randomised controlled trials of vasopressors for septic shock¹³

Intervention	No. of studies	No. of patients	RR (95% CI)
Noradrenaline + dobutamine v adrenaline	2	52	0.98 (0.57–1.67)
Noradrenaline v dopamine	3	62	0.88 (0.57–1.36)
Vasopressin v placebo	2	58	1.04 (0.06–19.33)

efficacy of various vasopressors continue to dominate the literature, and recommendations and use of vasopressors have changed markedly over the past 20 years. In global terms, where access to drugs such as noradrenaline, dobutamine, dopamine and vasopressin remains limited, there would appear to be an imperative to conduct a large-scale, high-quality mortality-based trial of catecholamines in circulatory shock.

Which catecholamines?

There is no consensus on the “best” inotrope/vasopressor for the treatment of shock. Even the summaries of recommendations published by eminent evidence-based organisations come to conflicting conclusions. The Cochrane Collaboration concluded, on the basis of evidence published before their systematic review in 2004, that dopamine and adrenaline are primarily suitable for all kinds of shock, with some consensus that noradrenaline be regarded as a second-line agent.¹³ The Surviving Sepsis Guidelines concluded that either noradrenaline or dopamine is the first-line vasopressor to correct hypotension in septic shock, with caution about the use of adrenaline.¹¹ Furthermore, a large observational European study suggested that the use of dopamine was associated with a higher mortality in patients with septic shock.¹⁵ Given this uncertainty, and the lack of definitive evidence, a prima-facie case can be made to conduct a large, pragmatic, simple trial of the two naturally occurring catecholamines, noradrenaline and adrenaline; there appears adequate equipoise in the literature, and the results would be generalisable to all countries.

What end-point?

The primary outcome measure for a definitive study of catecholamines should be an appropriate patient-centred outcome. As most patients who receive vasopressors have sepsis, all-cause 90-day mortality remains the “gold standard”, with important secondary outcome measures being resolution of shock and associated organ failure, and hospital length of stay. However, the determination of an appropriate

drugs were shown to be superior in controlled trials, and clinicians are left with uncertainty about patient-centred benefits or harm attributable to a particular vasopressor, and must therefore rely on clinical experience to guide patient management.

This quandary is not unique. Many established and accepted treatments in intensive care medicine have not been, and are unlikely ever to be, subjected to the scrutiny of high-quality randomised controlled trials. The question whether this is required for vasopressor therapy remains unanswered. However, an emerging body of evidence may soon provide some definitive outcome data.

Research priorities for catecholamines in shock

The imperative for a large-scale trial of vasopressors

The prompt recognition and correction of shock is associated with improved outcomes in selected patients. There is therefore an imperative to develop the most generalisable, applicable and cost-effective strategies to treat this common problem. This was highlighted in the Saline vs. Albumin Fluid Evaluation (SAFE) Study,¹⁴ where equivalent mortality was demonstrated in patients resuscitated with albumin or saline in the intensive care unit. With the exception of patients with burns or traumatic brain injury, the SAFE Study provides clinicians with a scientifically valid basis to select albumin or saline for fluid resuscitation in accordance with local pragmatic and cost considerations, rather than concerns about efficacy or safety.

There is no equivalent study for inotrope or vasopressor therapy. Strongly held views about the relative safety and

sample size to achieve these measures requires definitive phase II or preliminary outcome data, which simply do not exist. Catecholamines were used before the advent of pharmaceutical regulation and are now off-patent, published surrogate outcome studies are of poor quality, and a phase II trial is unlikely to be funded. However, observational studies and emerging investigator-initiated studies outlined below will provide appropriate phase II data.

What method?

The SAFE Study provided a benchmark for conducting trials in intensive care medicine.^{14,16} A similar study of catecholamines should be conducted in accordance with the principles of high-quality methodology: a prospective, randomised, multicentre, multinational, adequately powered, double-blind study assessing the effect of two catecholamines on all-cause 90-day mortality. Inclusion criteria should be broad and pragmatic, potentially including all patients who require vasopressor therapy, with stratification for a diagnosis of sepsis. Analysis should be by intention-to-treat, with expected completion and follow-up rates >97%. Such a high-quality study would provide unequivocal evidence for the selection of an inotrope/vasopressor in critically ill patients.

Emerging evidence

Three large-scale studies of catecholamines have been completed — in Australia, France and Canada — while a fourth study is underway in Europe. All these studies are large-scale, prospective, randomised controlled trials directed at patient-centred outcomes. The publication of these four studies over the next 12 months will provide important information about the effects and practices of catecholamines in severe sepsis.

The CAT Study

The Australian “CAT” study is a prospective, multicentre, double-blind, randomised-controlled trial comparing the effects of adrenaline and noradrenaline on resolution of shock in 280 intensive care patients. This study was completed in 2006 and demonstrated no difference in the resolution of shock between adrenaline and noradrenaline.

Other catecholamine studies

A prospective, multicentre randomised controlled trial from France has been completed. This study compared blinded infusions of adrenaline plus placebo versus noradrenaline plus dobutamine on resolution of shock and 28-day mortality in 250 critically ill patients. Preliminary presentations of these results did not demonstrate any differences in outcome measures between the two infusions.

A large-scale multicentre study compared the effect of noradrenaline versus noradrenaline plus low-dose, fixed-rate vasopressin (the Vasopressin vs Norepinephrine in Septic Shock Study — VASST) on 28-day mortality. Open-label noradrenaline was permitted once a threshold of 15 µg per minute was exceeded. Preliminary presentations of these results did not demonstrate any difference in mortality in the overall cohort, although some evidence of benefit was observed in patients with moderate levels of septic shock.

A third large-scale study currently underway was developed from an observational study of sepsis in European Intensive Care Units (the SOAP [Sepsis Occurrence in Acutely Ill Patients] Study).^{15,17} This study is comparing blinded infusions of adrenaline and dopamine (plus open-label drug for high-dose noradrenaline [$> 20 \mu\text{g}/\text{kg}/\text{min}$] and adrenaline [$> 0.19 \mu\text{g}/\text{kg}/\text{min}$]) on 28-day mortality.

The completion and publication of these four larger and high-quality methodological studies will provide important information about the clinical utility and efficacy of catecholamines on patient-centred outcomes. Clearly, these studies will supersede any other study or meta-analysis published to date.

However, all these studies have substantial limitations, particularly in power. The imperative to conduct a large-scale, pragmatic, generalisable, adequately powered, prospective, randomised controlled trial remains. The conduct and funding of such a study remains a great challenge.

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