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The Impact of Routine Norepinephrine Infusion on Hemodilution and Blood Transfusion in Cardiac Surgery

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Abstract

Background: Hemodilution and blood transfusion are associated with poor outcome after cardiac surgery. We hypothesized that routine norepinephrine infusion commenced prior to anesthesia induction during on-bypass cardiac surgery would reduce intraoperative hemodilution and red cell transfusion.

Methods: Two cohorts of consecutive cardiac surgery patients at different time periods were retrospectively reviewed for perioperative hemoglobin, creatinine concentrations and units of red cells transfused. Patients in group NE (n=72, in 2010) all received standardized hemodynamic management by a single anesthesiologist with low dose norepinephrine infusion commenced at 3-5 $\mu g.min^{-1}$ (18-30 $nmol.min^{-1}$, 0.24-0.4 $nmol.kg^{-1}.min^{-1}$) commencing prior to anesthetic induction and continued into the postoperative period. In the absence of blood loss, hemodynamic stability was achieved using vasopressors and inotropes rather than fluid administration, in an attempt to reduce hemodilutional anemia and trigger for red cell transfusion. Controls (n=94, in 2005) received selective norepinephrine infusion post cardiopulmonary bypass for persistent hypotension and vasodilation. There were no major changes to surgical or perfusion technique in the time period between cohorts, and the transfusion trigger remained the same at Hb<70 g/L.

Results: Intraoperatively, hemoglobin concentrations were higher in group NE compared with controls (p<0.0001) despite lower baseline values (139 ± 19 vs 133 ± 15, P=0.028). Additionally, fewer units of red cells were transfused in the NE group intraoperatively (0.2 ± 0.6 units/patient) compared with controls (0.53 ± 1.47, p=0.041). Maximum postoperative rise in serum creatinine concentration ($\mu mol.L^{-1}$) was not significantly different (NE 26 ± 32, controls 30 ± 57, p=0.49 and at discharge 3 ± 53 vs. 5 ± 30, p=0.39). NE group patients were at increased risk of bleeding, having received more extensive surgery (p=0.042), longer clamp-time (p=0.009) and no aprotinin compared to 74% of controls.

Conclusions: This study shows proof of concept that during on-bypass cardiac surgery, routine low dose norepinephrine infusion is associated with reduced hemodilution and intraoperative red cell transfusion without increasing postoperative serum creatinine.

Keywords: Cardiac surgery; Blood transfusion; Hemodynamic management; Anemia; Norepinephrine; Fluid restriction; Blood conservation

Introduction

During cardiac surgery, little blood is discarded, with most red blood cells (RBC) returned to the patient. Anemia is primarily caused by hemodilution from intravenous fluid administration as priming volume for the cardiopulmonary bypass (CPB) circuit, and as volume expansion to treat hypotension. Vasodilation is a common cause of hypotension and causes include the inflammatory response to surgery, anesthesia and CPB; which commonly persists postoperatively (9-44%) [1] as a result of systemic inflammation and sedative drugs. Venodilation leads to a relative central hypovolemic state due to expansion of the intravascular capacity. Hypotension is thus usually managed by fluid administration and boluses of short acting vasopressors. Hemodilutional anemia frequently occurs from fluids, CPB prime, cardioplegia, platelets and fresh frozen plasma if required. Vasoconstrictors such as norepinephrine (NE) are generally reserved for hypotension resistant to further fluid challenge or persistent low systemic vascular resistance [1,2]. Vasoconstrictors such as NE are often avoided due to concerns of undesirable vasoconstriction of renal, splanchnic and even arterial coronary bypass conduits including radial arteries, without good supporting evidence.

The rationale for pre-emptive routine NE before anaesthetic induction is to maintain normal vascular tone and capacitance rather than cause supranormal vasoconstriction. There is usually little blood loss before CBP and the principal cause of hypotension is vasodilation from anesthesia and commencement of CPB. Since the vascular space is not expanded, there is no need for fluid administration.

The key trigger for transfusion is the hemoglobin (Hb) concentration and not a reduction in the total red blood cell (RBC) mass, or the metabolic or physiologic performance of the patient. These triggers are based on guidelines, rather than a clinically related measurement of the patient at the time and may lead to RBC transfusion despite lack of blood loss [3].

The transfusion trigger has progressively been lowered due to evidence of increased morbidity and mortality associated with RBC

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transfusion and reduced blood viscosity (and associated theoretical increased flow) during CPB [3-6]. However, the Hb threshold for vital organ tissue oxygenation is unknown, and is influenced by patient comorbidities. Accumulating evidence of morbidity and mortality associated with hemodilutional anemia raises concerns about where to strike the balance between blood transfusion versus anemia [6,7,9-14]. Published guidelines on blood conservation during cardiac surgery from expert working groups recommended routine prevention of hemodilutional anemia during cardiac surgery [3,15-17].

We hypothesized that routine use of low-dose NE intraoperatively would reduce hemodilutional anemia and the need for red cell transfusion.

Patients and Methods

This study was approved by the Melbourne Health ethics committee as an audit of hospital practice and requirement for informed consent was waivered.

In this retrospective cohort study, data was retrieved and compared from databases and medical records from consecutive patients who underwent on-CPB cardiac surgery by a single surgeon at the Royal Melbourne and Melbourne Private Hospitals over two separate 12-month periods, 5 years apart. Data from a 12 month consecutive cohort in 2010, when intraoperative NE infusion was used routinely (NE group), was compared to a consecutive cohort in 2005 when NE was reserved only for persistent hypotension and vasodilation after CPB. In the NE group, NE infusion was commenced at 3 $\mu g.min^{-1}$ (18 $nmol.min^{-1}$ or 0.24 $nmol.kg^{-1}.min^{-1}$) prior to anesthesia, to prevent associated vasodilation, and continued intraoperatively until transferred to ICU. The infusion was adjusted to maintain desired mean arterial pressure (70-90 mm Hg) with minimal use of intravascular fluids. The aim was to prevent vasodilation and consequent fluid administration in an effort to reduce hemodilutional anemia and RBC transfusion. This technique was developed in 2006-2009 but only became routine in 2010. The principal reason to use the 2005 and 2010 cohorts was to compare a group without this technique (2005) to a group in 2010 when the technique was mastered and used routinely in all patients. Over this interval of approximately 5 years, surgical technique and restrictive fluid management remained the same. The intraoperative RBC transfusion trigger also remained the same (Hb less than 70.0 $g.L^{-1}$). The intravenous fluids used included Hartmanns crystalloid (Baxter, NSW, Australia), Gelofusin (Bbraun, Switzerland), Plasma-lyte 148 for CPB (Baxter, NSW, Australia) and 4% Normal serum albumin (CSL Biotherapies, Broadmeadows, VIC, Australia). Intravenous starches were not used.

Data were reviewed retrospectively by investigators not involved in medical care of the subjects. Baseline characteristics recorded included age, gender, height, weight, history of diabetes mellitus, NYHA classification, and type of surgery (CABG, valve, aorta, redo-sternotomy). Intraoperative data recorded included antifibrinolytic drug administration, intraoperative hemofiltration, postoperative centrifugal hemoconcentration of CPB blood, and the duration of CPB and aortic cross-clamp. Preoperative hemoglobin and creatinine (Cr) measurements were taken in the pre-operative clinic in the weeks leading up to elective surgery or on the day of hospital admission for urgent surgery. Hemoglobin was subsequently recorded after induction of anesthesia prior to CPB, after commencement of CPB, the lowest during CPB and on transfer to ICU. Creatinine was recorded on the day of discharge and the highest postoperative measurement. The number of units of RBC's transfused intraoperatively was recorded.

All patients were operated on by the same surgeon under similar conditions at the two hospitals. Anticoagulant medications were discontinued prior to surgery when possible to minimize bleeding from reversible coagulopathy (intravenous heparin at least 6 hrs, warfarin 5 days, antiplatelet drugs 1 week). General anesthesia was induced with midazolam, fentanyl, and propofol, and maintained with desflurane (1 MAC) and pancuronium was used for neuromuscular blockade. Analgesia included high thoracic epidural ropivicaine 0.2% and morphine 20 μ/mL, or intravenous fentanyl (5-10 μ/kg) when epidural contraindicated. Intraoperative monitoring included arterial, central venous and pulmonary artery pressure, intermittent cardiac output by thermodilution, 5 lead ECG, pulse oximetry, capnography, bispectral index EEG, nasopharyngeal temperature and transesophageal echocardiography.

In both groups, if hypertension was excessive, NE was reduced or temporarily ceased. No patient required commencement of a vasodilator to treat hypertension. For low cardiac index (<2.0 $L.min^{-1}.m^{-2}$), the initial inotrope added was dobutamine, with epinephrine or milrinone infusions administered infrequently. Anticoagulation was achieved with heparin 300-400 IU/kg of body weight and ACT>480 seconds was required before initiating CPB. The CPB circuit was primed with 2 L of

Variable	Control n=94	NE n=72	p
Age; years	67 (11)	66 (12)	0.456
Male (%)	78	64	0.081
Height; m	1.68 (0.1)	1.68 (1.1)	0.711
Weight; kg	81.0 (16.3)	78.4 (16.6)	0.306
Diabetes mellitus (%)	33	40	0.415
NYHA (%) **1-2** **3-4**	 64 36	 63 37	 0.872 0.872
Baseline preopHb; $g.L^{-1}$ **Baseline preop Cr; $mmol.L^{-1}$**	139 (19) 116 (84)	133 (15) 83.8 (55)	0.028* 0.006*

Values are mean (SD) or number (proportion).*p<0.05
NE: Norepinephrine group; NYHA: New York Heart Association; Hb: Hemoglobin concentration; Cr: Creatinine concentration

Table 1: Pre-operative characteristics of control and norepinephrine group patients.

Variable	Control n=94	NE n=72	p
Type of surgery			
Isolated CABG (%)	61	44	0.042*
Valve/complex (%)#	39	56	0.042*
Aortic aneurysm (%)	2	1	1
Aortic dissection (%)	0	3	1
All CABG (%) **Total arterial grafts (%)** **Radial artery used (%)**	65 95 95	51 100 97	0.151 0.550 1
CPB time, min	99.6 (47.9)	114.5 (46.6)	0.046*
Aortic cross-clamp, min	73.9 (42.1)	90.9 (39.7)	0.009*
Aprotinin (%)	74	0	<0.0001*
Hemofiltration on-CPB (%)	10	4	
Hemoconcentration post-CPB (%)	12	97	0.234
Postoperative hemofiltration for renal failure in ICU (%)	14	4	<0.0001*
Mortality n (%)	1 (1.1)	1 (1.4)	0.06 1

Values are mean (SD) or number (proportion). *p<0.05, #Valve ± CABG/redo, multiple valves or aortic surgery.
NE: Norepinephrine group; CABG: Coronary Artery Bypass Grafting; CPB: Cardiopulmonary Bypass; ICU: Intensive Care Unit.

Table 2: Intraoperative data of control and norepinephrine group patients.

Plasma-lyte 148 crystalloid solution and maintained at a temperature of 34-35°C. Acute normovolemic hemodilution and retrograde autologous priming of the CPB circuit were not used. Cardiopulmonay bypass was achieved with aortocaval cannulation via median sternotomy at a flow rate of 2.3-2.5 L.min^{-2} and mean arterial pressure maintained between 70-90 mm Hg. After aortic cross-clamping, cardiac arrest was maintained by administration of tepid blood cardioplegia (induction blood:cardioplegia 4:1, maintenance 6:1 or 8:1 depending on serum potassium concentration) with both antegrade and retrograde delivery. The heparin was neutralized with protamine 4 mg.kg^{-1}. Intraoperative RBC scavenging was routine in both groups. Post CPB residual circuit blood was centrifugally hemoconcentrated selectively in control and routinely in NE group patients. All patients were transferred to ICU mechanically ventilated and sedated with a propofol infusion.

Coronary artery bypass grafting included total arterial revascularisation with mammary and radial arteries where possible. There was no change to the use of NE consequent on the use of arterial grafts; and this institution has used vasopressors with arterial grafts since 1995.

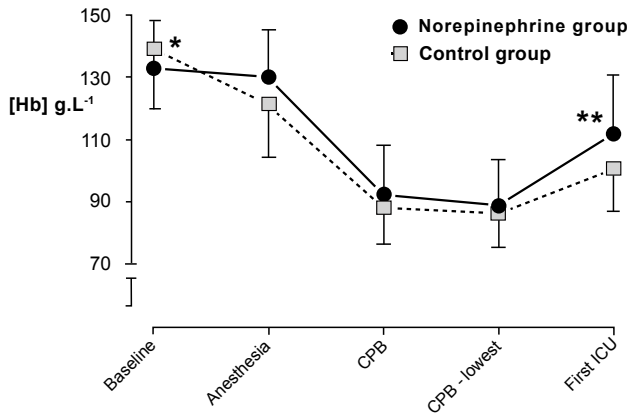

Figure 1: Comparison of mean hemoglobin concentrations of control (n=94) and norepinephrine (n=72) group patients. (Hb);meanHb, CPB;cardiopulmonary bypass, ICU;intensive care unit, *p=0.028, **p=0.0001.

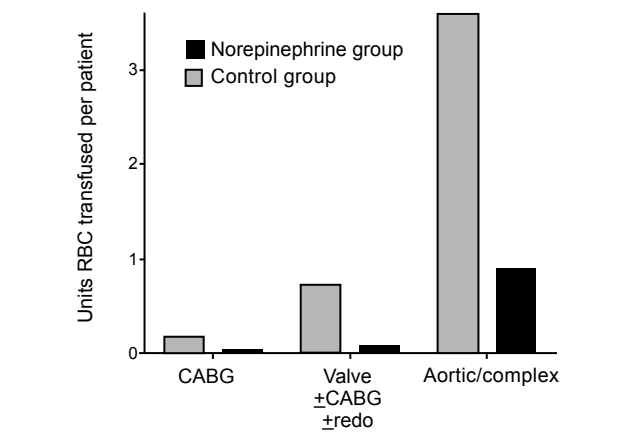

Figure 2: Units of RBC's transfused intraoperatively per patient for control (□, n=94) and norepinephrine (●, n=72) group patients. CABG: Coronary Artery Bypass Graft; RBC: Red Blood Cell.

Variable	Control Group n=94	NE Group n=72	p
Units RBC transfused	50	11	0.041*
Units per patient	0.53 (1.47)	0.15 (0.60)	0.041*
Patients transfused, n (%)	16 (17)	6 (8)	0.11
>4 RBC units, n (%)	5 (5)	1 (1)	0.37

Values are mean (SD) or number (proportion).
NE: Norepinephrine group; RBC: Red Blood Cells

Table 3: Intraoperative red blood cell transfusion requirements of control and norepinephrine group patients.

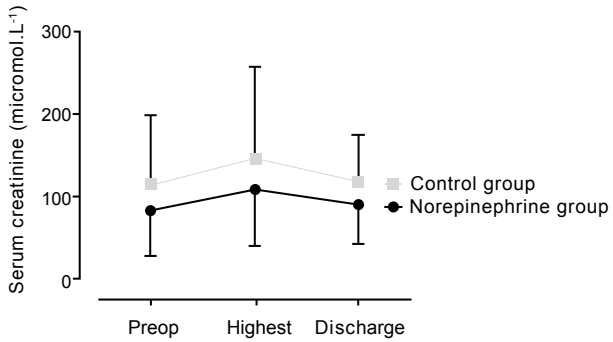

Figure 3: Changes in mean postoperative creatinine concentration of control (□, n=94) and norepinephrine (●, n=72) group patients. p=0.49.

The primary endpoint was the Hb concentration over the intraoperative period. The Hb on ICU admission was considered the final intraoperative measurement. Secondary endpoints included the number of units of RBC transfused, and the postoperative Cr rise from baseline.

Statistical Methods

Statistical analysis was performed using one-way mixed factorial repeated measured analysis of variance allowing for multisampling asphericity by applying either the Huynh-Feldt or Greenhouse-Geisser corrections for $\varepsilon<0.75$ and $\varepsilon>0.75$ respectively [18]. This allowed for a comparison of continuous variables over time. Continuous data and categorical data were compared with Student's two-tailed t test and Fisher's exact test respectively. Data were coded and stored in Microsoft Excel 2010 and analysed using SPSS V20 (SPSS Inc, Chicago, IL, USA). Statistical significance was defined as a value of $p<0.05$.

Results

Of the 171 patients retrieved from the hospital databases who received on-bypass cardiac surgery from the investigators, there were 2 patients from each group excluded due to missing hospital records and one patient excluded from the NE group due to incorrect surgical coding leaving 94 patients in the control group and 72 patients in the NE group for analysis. Preoperative data is presented in Table 1, intraoperative data in Table 2 and transfusion data in Table 3. NE group patients had more complex surgery (p=0.042), longer duration of CPB (114.5 ± 46.6 vs. 99.6 ± 47.9 min, p=0.046) and cross clamp (90.9 ± 39.7 vs. control 73.9 ± 42.1 min, p=0.009). The control group had a higher baseline Hb (p=0.028) and Cr (p=0.006). Aprotinin was used more frequently in the control group (74% vs 0%); as it was withdrawn from hospital use in the time between cohorts. No other antifibrinolytics or parenteral synthetic hemostatic agents were used.

After surgery, centrifugal hemoconcentration of residual CPB blood occurred more frequently in the NE group than the control group (97% vs. 12% p<0.0001). Other recorded characteristics were similar between groups. The patients receiving CABG surgery were similar in both groups as were the proportions receiving total arterial revascularisation and radial artery grafting.

The Hb was better preserved in the NE group than controls (p<0.0001, Figure 1). The greatest difference between groups was at the completion of surgery and transfer to ICU (NE group Hb 111.9 ± 18.7, control group Hb 100.7 ± 13.7, p<0.0001). There were fewer units of RBCs, transfused per patient in the NE group (p=0.041, Table 3 and Figure 2) during the intraoperative period. Despite a higher baseline Cr in the control group, the maximum increases in postoperative Cr from baseline were not different (NE group 26 ± 32, vs. control 30 ± 57 mmol.L^{-1}, p=0.49, Figure 3). However there was a non-significant trend towards more postoperative hemofiltration in the control group (14% vs. 4%, p=0.06).

Discussion

This study shows proof of concept that routine use of NE infusion to counteract vasodilation from anesthesia, CPB and surgery may assist in restrictive fluid management during on-bypass cardiac surgery. We found less intraoperative hemodilution and intraoperative red cell transfusion in patients who received NE infusion throughout anesthesia. These findings occurred despite a higher baseline Hb, less complex surgery and shorter CPB times in the control group. Routine infusion of NE was not associated with increased Cr.

The use of NE or a restrictive fluid strategy was not controlled in the ICU and therefore adherence to the technique was variable. Our data does not therefore allow us to comment on the efficacy of the strategy throughout the hospital stay, and we have restricted the primary endpoint to the intraoperative period up to the time of ICU admission. Further research is required to identify if maintenance of the vasopressor infusion to normalize vascular resistance prior to fluid administration will result in less anaemia and fewer transfusions over the entire perioperative period.

A degree of hemodilution is inevitable with use of CPB, due to the pump prime volume of 2 L of fluid. However, the anesthetic, CPB and surgery commonly results in a systemic inflammatory response, vasodilation, hypotension and a normal or increased cardiac output [19-21]. The traditional treatment is to initially administer intravenous fluids and to reserve vasopressor infusion (such as NE) when intravenous fluids are no-longer effective. This results in hemodilution which may trigger RBC transfusion, both of which are independent predictors of morbidity and mortality in cardiac surgery [5,11,22-24]. In this study the aim of NE infusion was to maintain venous and arterial vascular tone to prevent hypotension and maintain the normal vascular space volume, thereby facilitating a fluid restrictive strategy to minimize hemodilutional anaemia and RBC transfusion.

The intraoperative RBC transfusion trigger of 70 g.L^{-1} was used in both groups, and so the reduced intraoperative transfusion in the NE group is likely to be due to better preservation of Hb concentration from less hemodilution. In a small randomized trial, Vretsakis et al. demonstrated reduced red cell transfusion in 100 patients with a fluid restrictive strategy compared with 92 controls with similar risk factors for bleeding [25]. Recommended techniques to prevent hemodilutional anemia include minibypass circuits, retrograde autologous priming of blood, ultrafiltration during CPB and microplegia [3], however to date we are unaware of any reports of using routine vasoconstrictors to minimize hemodilution. The optimal conditions for blood function include normal concentration and temperature. A low Hb is a marker for dilution of all of the blood components and it may be expected that all functions of blood including clotting may be affected.

The mean Hb was higher in the NE group than controls at all four intraoperative periods but the most marked difference was on arrival in ICU. The Hb increased in both groups from CPB-lowest to transfer to ICU due to the transfusion of residual CPB blood. The greater rise in the NE group may have been due to more frequent centrifugal hemoconcentration of residual CPB blood prior to re-transfusion (97% v 12%). However, this does not account for the higher Hb concentrations at the other 3 time periods.

There are concerns that NE may exacerbate CPB associated renal dysfunction by potential regional vasoconstriction, and it is usually reserved for persistent postoperative hypotension and vasodilation [26,27]. However this was not evident in this study. In fact there was a non-significant trend of increased postoperative hemofiltration in the control group. This may have been contributed to from their higher baseline Cr and frequent use of aprotinin (associated with renal injury) [28]. Similar findings were found by Morimatsu et al. who reported no difference in postoperative Cr between 100 on-bypass cardiac surgery patients with postoperative vasodilation treated with NE compared with 100 similarly matched controls without NE [29]. In this study, pre-emptive low dose NE infusion was used in the NE group to prevent vasodilation and hypotension by titration to blood pressure and cardiac output measured by a pulmonary artery catheter. There is a risk that routine NE use may contribute to excessive vasoconstriction and reduced cardiac output if this is not monitored.

One key concern amongst some surgeons is the belief that use of vasoconstrictors may cause arterial coronary bypass grafts to spasm and fail. There is little if any evidence for this, and the concept arose from the original paper by Acar who postulated that a key reason for the early failure of radial artery grafts in the 1970s was spasm and he recommended the use of calcium channel antagonists to prevent vasospasm [30,31]. This became standard practice for radial artery grafts. In our institution however, we have used vasopressors after CPB and in the ICU since 1995. Our practice is routine total arterial revascularisation where the majority of multivessel coronary grafting relies on the radial artery [32-34]. We reject the hypothesis that the use of vasoconstrictors that aim to restore a vasodilated state toward normal vascular tone will result in spasm of these arterial grafts. This centre has one of the largest experiences in the world of radial artery grafting [33,35].

Limitations

Due to the retrospective study design the two groups are not identical. However, the NE group started with a lower Hb and had more complex surgery. If the groups had been equal there may have been a greater difference observed. An effort to minimize bias was made by performance of the study by research staff not involved in patient care, to capture whole cohorts, and to use a single surgeon. The Hb and RBC transfusion rates may have been influenced by differing anesthetic management, however it would be expected that a more restrictive transfusion strategy would result in lower Hb concentration. Total intraoperative blood loss and fluid administration were not recorded and hence hemodilution is therefore assumed rather than proven. It is possible that there was less intraoperative blood loss in the NE group; yet most intraoperative blood loss was scavenged into the CPB reservoir or the cell saver and thus not discarded in either group. Additionally,

the NE group patients were expected to be at greater risk of bleeding as they had more extensive surgery, longer CPB and aortic cross clamp times and less antifibrinolytics than the control group [36].

Conclusion

The routine use of low dose norepinephrine infusion to treat vasodilation was associated with less intraoperative anemia and reduced intraoperative red cell transfusion, without detrimental effect on renal function. However due to the retrospective nature of the study with a significant time interval between compared cohorts, this study provides feasibility and proof of concept only. However the study supports a randomized trial as it may offer a simple and cost effective method of reducing blood transfusion that may be easily applied.

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