**Refusal of blood products for CPB – implications for AKI?**

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A relatively small percentage of patients presenting for cardiac surgery refuse transfusion of blood products primarily on religious grounds, particularly followers of the Jehovah's Witness (JW) faith. The basis for this belief is from a literal interpretation of three biblical passages from the old and new Testament[1]. The basic position of refusal of red cells, white cells, plasma and platelets was further elucidated with the advent of blood fractions and recombinant products such that acceptance of these fractions has become a "conscience decision" by followers of the JW faith (1). While use of blood substitutes such as perfluorocarbons and haemoglobin-based oxygen carriers is referred to in JW literature as an acceptable alternative to transfusion of blood products, these are yet to gain widespread use (2). The right to refuse blood products in Australia and New Zealand is enshrined in legislation on informed consent and under the Australian Charter of Healthcare Rights and the New Zealand Code of Health and Disability Services Consumers' Rights. The latter is very specific and Right 7 details the right to informed consent, to refuse treatment and to use an advance directive under common law. Treating without consent has ramifications under criminal and tort law, disciplinary liability by registered professional bodies and liability under the Code of Rights.

The majority of reports of cardiac surgery in Jehovah's Witnesses refusing blood transfusions are single centre experience with relatively small numbers of patients (3-8). This is a reflection of the ratio of JWs to the population (USA 0.6%, Aust/NZ 0.3%). There is just one recent meta-analysis of 6 studies comparing outcomes of 564 JWs with 903 controls (9).

A 2010 comparative report of outcomes in JWs undergoing CPB in Australia by Bhaskar and colleagues details the conduct of cardiopulmonary bypass as *"…ultra-filtration and administration of diuretic drugs were liberally applied to avoid excessive haemodilution as a result of the addition of cardioplegia solution during CPB. Extracorporeal circulation was performed with moderate hypothermia (30 ◦C), maintaining the pump flow between 2.6 and 3.0 l* $min^{-1}m^{-2}$*"*(10). This paucity of accurate CPB data is typical of such reports and is as scant in detail as the first report of cardiovascular surgery in Jehovah's Witnesses from the Texas Heart Institute in 1977(3). The Australia and New Zealand Collaborative Perfusion Registry (ANZCPR) established in 2007 is unique in that it acquires data electronically in 20-30 second epochs during CPB together with preoperative variables

[1] i) Genesis 9:4, 'But you shall not eat flesh with its life, that is, its blood.'

(ii) Leviticus 17:10, 'If any one of the house of Israel or of the strangers who sojourn among them eats any blood, I will set my face against that person who eats blood and will cut him off from among his people.'

(iii) Acts 15:29, ' . . . that you abstain from what has been sacrificed to idols, and from blood, and from what has been strangled, and from sexual immorality. If you keep yourselves from these, you will do well.'

and postoperative outcomes and now contains more than 30,000 procedures from 9 contributing centres (11). The ANZCPR has been used for benchmark and quality improvement initiatives including red cell reduction in CPB and more recently the relationship of DO2 on renal outcome (12, 13).

The aim of this study was to investigate the management of modifiable factors of CPB on renal outcome in patients refusing blood transfusion compared to a matched cohort of patients accepting blood transfusion.

**METHODS**

Nine cardiac surgical centres in Australia and New Zealand prospectively collected data using the ANZCPR as previously described (11). Institutional Ethics Review Board approval was obtained at each participating centre, and this study was approved by the ANZCPR Steering Committee. The ANZCPR meets the Australian Commission on Safety and Quality in Health Care National Operating Principles for Australian Clinical Quality Registries; http://www.safetyandquality.gov.au/our-work/information-strategy/clinicalquality-%20%20registries/strategic-operating-principles-for-clinical-quality-registries/. Clinical data definitions were based on the Australian and New Zealand Society of Cardiothoracic Surgeons registry (14). Complete ANZCPR variable definitions are available at www.anzcpr.org. Combined morbidity was defined as the incidence of postoperative ventilation >48hrs, acute renal failure, stroke or return to theatre.

Centres collected data on 34,884 adult patients undergoing CPB between January 2007 and December 2018. Patients were excluded if they were missing data on the refusal of blood product transfusion, preoperative haemoglobin or transfusion data yielding an initial data source of 30,942 patients, 118 of which were identified to have refused transfusion that were included in the study. A propensity matched group of patients accepting transfusion was identified to compare differences in intraoperative practice and outcomes. (see preoperative variables Table 1)

| | Control | JW | p |
|---|---|---|---|
| Age, median (IQR) § | 66.5 (59, 73) | 68 (59, 75) | 0.42 |
| Female ¶ | 31% | 31% | 1.00 |
| BMI, median (IQR) § | 29.32(25.05, 33.45) | 29.64 (25.50, 32.62) | 0.89 |
| Resp_disease ¶ | 14% | 13% | 0.85 |
| Redo ¶ | 13% | 8% | 0.29 |
| Diabete ¶s | 34% | 33% | 0.89 |
| Hypertension ¶ | 69% | 73% | 0.47 |
| CHF ¶ | 16% | 16% | 1.00 |
| Severe LV ¶ | 4% | 4% | 1.00 |
| Emergency ¶ | 2% | 1% | 0.56 |
| CVD ¶ | 7% | 8% | 0.62 |
| MI ¶ | 36% | 31% | 0.49 |
| Hb preop, median (IQR) § | 135 (125, 146) | 135 (122, 146) | 0.85 |
| Creat pre, median (IQR) § | 81 (71, 98) | 88 (74, 106) | 0.086 |
| EU score, median (IQR) § | 3.69 (1.83, 6.61) | 3.31 (1.99, 5.5) | 0.78 |
| CABG ¶ | 51% | 50% | 1.00 |
| MV surgery ¶ | 7% | 7% | 1.00 |
| AV surgery ¶ | 14% | 14% | 1.00 |
| Other ¶ | 14% | 14% | 1.00 |
| AVR+CABG ¶ | 10% | 10% | 1.00 |
| MVR+CABG ¶ | 4% | 4% | 1.00 |
| § = Wilcoxon rank-sum ¶ = Pearson's chi-squared | | | |

Table 1 Preoperative variables.

The primary endpoint was acute kidney injury (AKI) defined according to the serum creatinine criteria of the modified RIFLE (renal Risk, Injury, Failure, Loss of renal function and End-stage renal disease) classification.

Specifically, AKI is reported as any AKI (creatinine greater than 150% baseline), AKI-Risk (creatinine between 150-200% baseline) or AKI-Injury (creatinine greater than 200% baseline). Change in creatinine was measured from preoperative value to maximum postoperative value. The two patient groups were compared across time for the entire time period (2007 – 2018) and within 2 time periods; early (2007-2012 - 53 control v 53 JW) and late (2013-2018 - 65 control v 65 JW) for modifiable CPB variables and for outcome variables.

**Statistical Analysis**

STATA version 15.0 (StataCorp LP, College Station, Tx, USA) was used for all analyses. A propensity score for refusal of blood transfusion was calculated using the following preoperative variables; age, severe LV dysfunction, gender, emergency, body mass index, cerebrovascular disease, chronic obstructive pulmonary disease, myocardial infarction, reoperation, haemoglobin level, diabetes, creatinine, hypertension, congestive heart failure, procedure type, Euroscore, CPB time and the year of operation. Patients were propensity matched in a 1:1 ratio using nearest-neighbour matching (caliper 0.01) without replacement of subjects resulting in 118 matched pairs. Patient preoperative and perioperative characteristics were compared between cohorts according to an early (2007-2012) and late (2012-2018) time period and acceptance or refusal of transfusion. Differences between groups were assessed using the Wilcoxon rank sum test for continuous data, and the Pearson $\chi 2$ and Fisher exact test for categorical variables.

**RESULTS**

Modifiable factors of CPB are shown in table 2. 32% of patients in the control group were transfused a blood product of any kind over the total study period (2007-2018) with a non-significant reduction in the later period (2013-18) compared to the early period (36% and 29% respectively p=0.44 Pearson's chi-squared). Red cell transfusion was 37% and 23% of control patients for the two periods respectively.

| | 2007 - 2018 | | | 2007 - 2012 | | | 2012 - 2018 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Control n=118 | JW n=118 | p | control | JW | p | control | JW | p |
| NetPrime, median (IQR) § | 1410 (1160, 1610) | 1335 (1060, 1610) | 0.18 | 1610 (1400, 1625) | 1596 (1153, 1662) | 0.69 | 1290 (1100, 1602) | 1212 (1025, 1462) | 0.10 |
| Cell salvage ¶ | 34% | 70% | <0.001 | 25% | 67% | <0.001 | 42% | 72% | <0.001 |
| RAP ¶ ¶ | 26% | 44% | 0.005 | 26% | 43% | 0.073 | 26% | 45% | 0.028 |
| Hemofiltration ¶ | 3% | 8% | 0.15 | 4% | 11% | 0.14 | 3% | 5% | 0.65 |
| CPB_time, median¶ (IQR) § | 84 (65, 112) | 83 (66, 106) | 0.55 | 86 (65, 119) | 75 (52, 102) | 0.085 | 84 (65, 108) | 87 (71, 111) | 0.36 |
| Nasomin, median (IQR) § | 33.35 (32.1, 34.28) | 33.5 (32.25, 34.25) | 0.51 | 33.25 (32.1, 34.3) | 33.7 (32.8, 34.3) | 0.13 | 33.45 (32.6, 34.24) | 33.4 (32.2, 34.1) | 0.60 |
| MAPavg, median (IQR) § | 61.23 (55.92, 65.49) | 61.6 (55.73, 65.99) | 0.52 | 59.655 (54.14, 63.24) | 59.26 (54.98, 64.61) | 0.76 | 62.24 (58.14, 66.29) | 63.64 (58.67, 66.49) | 0.56 |
| Clavg, median (IQR) § | 2.276654 (1.99, 2.39) | 2.176912 (1.96, 2.39) | 0.17 | 2.269104 (2.02, 2.39) | 2.14 (1.96, 2.29) | 0.038 | 2.292607 (1.99, 2.39) | 2.25 (1.94, 2.45) | 0.96 |
| Hbmin_1, median (IQR) § | 88 (77, 99) | 90 (79, 99) | 0.40 | 85 (74, 95) | 84 (76, 96) | 0.69 | 93 (83, 100) | 95 (85, 102) | 0.38 |
| minDO2, median (IQR) § | 273.3358 (239.91, 304.71) | a271.92 (244.78, 304.46) | 0.93 | 263.41 (233.14, 286.69) | 256.16 (232.23, 283.25) | 0.51 | 285.68 (246.82, 311.19) | 287.40 (259.55, 324.57) | 0.56 |
| Lacmax, median (IQR) § | 1.7 (1.2, 2.3) | 1.65 (1.3, 2.15) | 0.69 | 1.8 (1.5, 2.5) | 1.7 (1.3, 2.6) | 0.51 | 1.45 (1.1, 2.1) | 1.5 (1.1, 2) | 0.89 |
| AnyTrans ¶ | 32% | 0% | <0.001 | 36% | 0% | <0.001 | 29% | 0% | <0.001 |
| CPBTrans ¶ | 9% | 0% | <0.001 | 11% | 0% | 0.012 | 8% | 0% | 0.023 |
| ANTrans ¶ | 9% | 0% | 0.001 | 10% | 0% | 0.021 | 8% | 0% | 0.022 |
| ICUTrans ¶ | 27% | 0% | <0.001 | 33% | 0% | <0.001 | 22% | 0% | <0.001 |
| AnyRCC ¶ | 29% | 0% | <0.001 | 37% | 0% | <0.001 | 23% | 0% | <0.001 |
| § = Wilcoxon rank-sum ¶ = Pearson's chi-squared | | | | | | | | | |

Table 2. Modifiable factors of CPB

The use of cell salvage was significantly higher in the JW group compared to matched controls over the entire period and within both the early and late time periods (70% V 34% p=<.001, 67% v 25% p=<0.001 and 72% v 42% p=<0.001).

Of the CPB modifiable variables relating to haemodilution there was no difference in nett prime volume between the control group and the JW group within either the early or the late period. There was a significant reduction in nett prime volume for both groups in 2013-18 compared to the earlier period (1610ml to 1290ml p=<0.001 and 1596ml to 1212ml p=<0.001 respectively). The use of retrograde autologous priming (RAP) was higher in JWs (44% v 26%, p=0.005) over the entire period and for the more recent period (45% v 26%, p=0.028) however the volume of RAP from the CPB circuit was significantly higher only in the 203-2018 period (540ml v 350ml p=0.035). Hemofiltration use was no different between the two groups at any time point and was low at less than 10% of patients.

Minimum Hb during CPB was no different between the 2 groups in either time period but increased significantly for both JWs and Controls over time (84.5 g/L v 95 g/L p=0.003 and 85 g/L v 93g/L p=0.007).

Of the primary determinants of minimum DO2 (assuming 100% SaO2); Flow Index (median flow average 2.3 and 2.2Lmin$^{-1}$m$^{2}$) and minimum Hb were no different between JWs and controls in either the early or late period, however the increase in minimum Hb over the two time periods is reflected in the significant increased DO2i for both the control group (263.41 v 285.68 p=0.011) and the JW group (256.16 v 287.40 p=<0.001). Of note while both groups were below the DO2i threshold of 270mlmin$^{-1}$m$^{2}$ for elevated renal injury (14) in the early period, the $DO_2i$ for the entire period was 273 and 272 for the control and JW group respectively.

Mean arterial pressure (MAP) was not different between the control group and the JW group for any time interval however both groups showed a significant albeit small increase in later period compared to the early period (59.7 v 62.2mmHg p=0.027 and 59.2 v 63.6 mmHg p=0.015)

Outcomes are shown in table 3. The primary end point AKI of Rifle Class R or greater in this analysis showed no difference between JWs refusing transfusion and the control group in either the early (13% v 11% respectively) or the more recent time period (11% v 6% respectively) or indeed over the total time period (10% v 8%).

| | Control n=118 | JW n=118 | p |
|---|---|---|---|
| Year ¶ | | | 0.76 |
| Creat50 ¶ | 10% | 8% | 0.72 |
| Creat100 ¶ | 4% | 4% | 0.71 |
| ICU Bld loss, median (IQR) § | 200 (130, 300) | 150 (97.5, 200) | <0.001 |
| ICU time, median (IQR) § | 10.2 (6, 18) | 9 (7, 16) | 0.67 |
| Ventilation >48 hr ƒ | 4% | 4% | 0.71 |
| LOS post op, median (IQR) § | 7 (6, 11) | 6 (5, 8) | <0.001 |
| Post op IABP ƒ | 0% | 3% | 0.083 |
| Reop ƒ | 4% | 4% | 0.99 |
| MI post op ƒ | 3% | 1% | 0.31 |
| Post op Dialysis ƒ | 5% | 1% | 0.091 |
| Stroke ƒ | 1% | 2% | 0.57 |
| Dialysis ƒ | 3% | 0% | 0.083 |
| Death ƒ | 1% | 3% | 0.19 |
| ARF ¶ | 10% | 8% | 0.49 |
| Morbidity ¶ | 15% | 13% | 0.66 |
| § = Wilcoxon rank-sum ¶ = Pearson's chi-squared ƒ=Fisher's Exact | | | |

In terms of surgical modifiable factors for AKI, bypass time, cross clamp time and reoperation were controlled for in the matching criteria. Four-hour postoperative blood loss was significantly lower in the JW group for the entire period and for the early time period (200ml v 150ml p=<0.001 and 250ml v 150ml p=<0.001) but not different between groups in the more recent period (155ml v 135ml p=0.085).

Table 3 Outcomes

Post-operative length of stay was significantly shorter in the JW group compared to the controls overall (7 days v 6 days p=<0.001). There was no difference in the measure of combined morbidity or mortality for JWs refusing blood products in this series compared to patients consenting to transfusion.

**DISCUSSION**

This study identifies modifiable components of perfusion practice from a large database of electronically acquired data in patients refusing blood products compared to patients consenting to transfusion. There was no difference in the primary endpoint of AKI in this series of patients who refused blood products compared to matched controls. While this is consistent with most other previously published comparative studies, this study reveals detail of CPB variables associated with renal outcome in patients refusing blood products not previously reported.

Unlike other studies we matched JW preoperative haemoglobin to the control group so CPB factors relating to haemoglobin such as the dilutional effect on $DO_2$ were not confounded. Of note a post-hoc analysis for the early and late time periods revealed no statistical difference in the preoperative haemoglobin between the JW group and 30054 non-JW patients from the ANZCPR database consenting to transfusion (132 v 131 g/L and 137 v 134 g/L). This is at variance to other studies that show JWs having higher preoperative haemoglobin.

Management of MAP during CPB remains controversial. In a recent RCT Kandler and colleagues using electronic data acquisition found no difference in AKI in coronary artery bypass patients randomised to a MAP greater or less than 60mm Hg (15). Our study showed no difference in the management of MAP during CPB between the JW group and matched controls with a median average CPB MAP of just below and just above 60 mmHg in the early and late periods of the study.

Not surprisingly use of cell salvage in JW patients was approximately double that of matched controls. More interestingly we saw a shift over time to more aggressive use of RAP likely contributing to reduced nett prime volume as well as the evolution of smaller prime CPB circuits and a shift to higher nadir haemoglobin. The importance of $DO_2$ index on AKI has received recent attention and this study reveals a shift in DO2i from a level below the 270 threshold prior to 2013 to significantly above this threshold in the 6 years to 2019. Interestingly this shift is not due to a change in CPB flow, that remains consistently at a median average of a 2.2/2.3 index, but to the increase in minimum haemoglobin in the later period.

Post-operative blood loss was lower in the JW group compared to matched controls as was post-operative length of stay. These outcomes in JWs undergoing cardiac surgery are consistent with other studies again consistent with other studies (7, 9, 16) and an enhanced focus on haemostasis with strategies including meticulous surgical technique do not impact costs of hospital stay (7).

Apart from not accounting for addition of crystalloid fluids, limitations include this being a retrospective study of prospectively collected data as opposed to an RCT and the small number of patients who refuse blood products limiting the size of the study population. The ANZCPR does not record cause of death. We do not collect data on addition of crystalloid perioperatively and restriction of fluid addition in JWs likely plays a part in the haemodilution picture.

A management strategy plan in a recent review of perioperative Jehovah's Witnesses (2) refusing blood transfusion bares very close resemblance to current published guidelines on blood management for cardiac surgical patients (17, 18). There was no difference for JWs in morbidity or mortality in this series.

**CONCLUSIONS**

Refusal of blood products in cardiopulmonary bypass patients does not negatively impact postoperative AKI (or mortality) compared to patients accepting transfusion. Strategies for blood conservation JW patients refusing blood products should be similarly applied to patients who consent to transfusion.

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