**A Single-centre Review of Iatrogenic Anaemia in Adult Intensive Care**

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**ABSTRACT**

**Objectives:** 1) quantify the volume of diagnostic blood loss (DBL) and evaluate its impact on intensive care unit (ICU) patients; 2) examine the correlation between severity of disease and DBL; 3) identify potentially vulnerable patient subgroups.

**Background:** Iatrogenic anaemia is an important problem amongst ICU patients, with significant daily DBL.

**Methods:** Single-centre observational cohort study conducted at St George’s Hospital, London cardiac and general ICU. 40 patients were included in the study. Variables measured: volume of blood collected and discarded on a daily basis; Acute Physiology and Chronic Health Evaluation (APACHE) II score; frequency of phlebotomy; haemoglobin concentration before and after admission to ICU; reason for admission; and complications developed in ICU.

**Results:** Mean (SD) total volume drawn per patient per day over 4 days was 86.3mL (19.58). Nearly 30% of the total blood taken was discarded. There was a strong positive correlation between: patients admitted because of sepsis and volume of DBL (p<0.01); APACHE II score and volume taken (p=0.01); patients who developed respiratory failure requiring ventilation and volume taken (p<0.01); and patients who had received a blood transfusion and volume taken (p<0.01). Haemoglobin concentration on discharge was negatively associated with DBL volume (p<0.01).

**Conclusion:** High volumes of blood were taken and discarded from the study population, possibly reflecting the fact that there are no guidelines for ICU staff in terms of the amount of blood that needs to be withdrawn in order to ‘prime’ access lines.

**Key words:** diagnostic blood loss, iatrogenic anaemia, adult intensive care, blood transfusion, patient blood management

**INTRODUCTION**

It is well established that anaemia of any cause has a significant impact on patient morbidity and mortality (Collins et al, 2000; Culleton et al, 2006; Nissenson et al, 2003). ‘Iatrogenic anaemia’ is ‘a condition of lowered haematocrit and haemoglobin count resulting from large or frequent removal of blood samples, usually for laboratory testing’ (Stefanini, 2014). The idea of iatrogenic anaemia or ‘nosocomial anaemia’ was first put forward in 1973 to describe the decrease in haemoglobin that was observed in patients admitted to intensive care (Eyster and Bernene, 1973). It is now recognised that blood loss from phlebotomy is independently associated with the development of hospital-acquired anaemia (Salisbury et al, 2011). Therefore, strategies that aim to reduce the frequency and volume of phlebotomy are important (Levi, 2014).

Patients in intensive care units (ICU) clearly represent the most acutely unwell population in a hospital and generally require long stays as in-patients (Williams et al, 2010) and a high frequency of diagnostic blood tests (Vincent el al, 2002). Evidence suggests that during an admission to ICU, patients lose 41mL (SD 39.7) each day for diagnostic tests (Vincent et al, 2002), with a median blood loss of 200mL over the course of their admission (Wisser et al, 2003). Moreover, these patients often rely on collection of blood through long peripheral and central lines which can lead to high volumes of blood being discarded prior to filling sample tubes (Coene et al, 2015). Whilst ICU patients undoubtedly require careful monitoring through diagnostic blood tests, a substantial number develop anaemia (Astin and Puthucheary, 2014; Walsh and Saleh, 2006).

There was no local guidance about iatrogenic anaemia at our centre at the time of this work which was a contributing factor for undertaking this study.

**MATERIAL AND METHODS**

Data for this single-centre observational cohort study (supported by NHS Blood and Transplant) were collected at St George’s Hospital, London, cardiac intensive care unit (CICU) and general intensive care unit (GICU). All patients included in the study had been admitted to CICU/GICU for at least 4 days. The study was conducted from December 1st 2015 to December 31st 2015 and consisted of a one-month observation of daily phlebotomy carried out by ICU nurses on 40 patients who were split between CICU and GICU. During this period, the daily number of blood samples taken from each of the 40 patients and sent to the laboratory for: full blood count (FBC); biochemistry; coagulation screen; blood cultures; and cross-match were recorded. Throughout this time, a survey was also completed by 20 ICU nurses. The primary aims of the survey were to establish the volume of blood ICU nursing staff discarded when they drew blood from a central line or peripheral line, as well as calculating the mean and cumulative volumes of blood taken per draw for FBC, coagulation screen, biochemistry, blood cultures and cross-match. Observation was carried out by one of the authors. The survey was conducted by asking direct questions to the nurses face to face at the bedside, during their daily practice of looking after patients in ICU. All the nurses interviewed were also asked to show how much blood was put in the tube and how much blood was discarded.

Further information about the 40 patients that comprised the study population was recorded using the ICU patient notes. This included: the primary reason for admission; the haemoglobin concentration on admission and discharge from ICU; the length of stay in ICU; and whether they received a blood transfusion whilst in ICU. Moreover, where possible, each patient’s APACHE II score was calculated. The data were then analysed using analysis of variance (ANOVA), independent t-test (two-tailed) and Pearson correlation coefficient (using p<0.05 to determine statistical significance) to examine the association between different variables and the volume of blood taken for phlebotomy.

**RESULTS**

*Patient demographics*

40 adult patients were included in the study. The mean (SD) age of the study population was 66 years (15) and the median (range) was 69 years (65). There were 31 male patients and 9 female patients. The mean (SD) length of stay in ICU was 15 days (13.9) and the median (range) was 10 days (70). 25 patients were admitted to GICU and 15 were admitted to CICU.

*Volume of blood taken*

The mean volume of blood taken per draw for FBC, biochemistry, coagulation screen, blood cultures and cross-match (as identified in the survey completed by 20 ICU nurses) were: 4mL, 4mL, 2.8mL, 5mL and 6mL, respectively. The mean volume of blood discarded from central or peripheral lines per patient per draw by ICU nursing staff is represented in *Figure 1*.The mean (SD) volume of blood taken for analysis per day was 61.6mL (8.4) and the median (range) volume was 60mL (40). The mean (SD) volume of blood discarded from cannulae and central lines per day was 24.7mL (3.7) and the median (range) volume was 24mL (16). Thus, the mean (SD) overall volume of blood taken per patient per day over the 4 days was 86.3mL (19.6) (*see Figure 2*).

*Haemoglobin concentration*

The mean (SD) haemoglobin concentration on admission to ICU was 103 g/L (20.5) and the mean (SD) haemoglobin concentration on discharge from ICU was 97 g/L (15); the mean (SD) difference in haemoglobin concentration between admission and discharge to ICU was -6.8 g/L (17). There was no association between either haemoglobin on admission and volume of blood taken or difference in haemoglobin and volume of blood taken (p=0.44 and p=0.07 respectively). There was a statistically significant negative association between haemoglobin on discharge and volume of blood taken (p<0.01). The mean (SD) blood circulating volume was 4.14 L (0.77).

*ICU admission*

There was no statistically significant correlation between age and volume of blood taken (p=0.80) or gender and volume of blood taken (p=0.26). There was a statistically significant difference between ICU department and volume of blood drawn, with GICU patients having larger volumes of blood taken by phlebotomy (p<0.01). There were 10 different reasons for admission to ICU: 8 patients were trauma cases; 7 patients had sepsis; 7 patients had respiratory failure; 5 were post-operative surgical patients; 5 patients had undergone aortic aneurysm or dissection repair; 2 patients had bowel obstruction; 2 patients had suffered cardiac arrest; 2 patients had a ST elevation myocardial infarction (STEMI); 1 patient had a non-ST elevation myocardial infarction (NSTEMI); and 1 patient had pulmonary oedema. Using ANOVA, a statistically significant association was demonstrated between reason for admission and volume of blood taken (p<0.01), with sepsis patients requiring the highest volumes of blood to be taken.

*Patient complications*

18 patients developed respiratory failure which required ventilation; 15 patients had acute kidney injury (AKI); 6 patients had an electrolyte abnormality; and 5 patients developed sepsis. There was a strong positive correlation between developing respiratory failure and volume of blood taken (p<0.01). There was no association between developing an AKI, sepsis, or electrolyte disturbance and volume of blood taken (p=0.54, p=0.64 and p=0.90 respectively). 19 patients required a blood transfusion, with a mean (SD) of 4.11 units (1.37) being transfused amongst these patients. There was a statistically significant correlation between having a blood transfusion and volume of blood taken for phlebotomy (p<0.01).

*APACHE II*

APACHE II scores were unavailable for 5 patients. The mean (SD) APACHE II score of the remaining 35 patients was 19.09 (5.93). There was a statistically significant association between APACHE II score and volume of blood taken (p=0.01).

**DISCUSSION**

A driving factor for undertaking this study was the Patient Blood Management (PBM) agenda in our organisation. PBM is ‘an evidence-based integrated multi-disciplinary team (MDT) approach to effectively manage and conserve a patient’s own blood loss, thus decreasing unnecessary exposure to transfusion’ (Bielby and Moss, 2018). PBM has been shown to be particularly effective in critically ill patients in an ICU setting (Shander et al, 2017). ‘Minimising blood loss’ is one of the three ‘pillars’ of PBM, the other two of which are ‘optimising the patient’s blood’ and ‘optimising the patient’s physiological tolerance of anaemia’.

*Principal findings*

The results of this study highlight that a considerable volume of blood (86.3mL) is being taken for phlebotomy each day from ICU patients in the first four days of admission. Perhaps most significantly, nearly 30% of blood drawn was discarded, with great variability in the discard volume amongst patients (range 16mL to 32mL). This highlights the fact that there are no local guidelines for taking blood from central lines or other access sites which then leads to high levels of wastage. However, it must be noted that whilst there has been some research into safe discard volumes from arterial lines (Davies et al, 2000, who advocate discarding 1.6mL), central lines (Cole et al, 2007, who advocate discarding 3mL) and peripheral cannulae (Baker et al, 2013, who advocate discarding 1mL), these studies have often focused on paediatric populations, and there is limited evidence available from adult populations. Hence there are no national or international standards for this practice.

The majority of patients admitted were elderly with a mean (SD) APACHE II score of 19 (5.9). Despite the fact that there was no correlation between age and the volume used for phlebotomy, there was a statistically significant association between APACHE II score and volume of blood drawn for diagnostic testing (p=0.01). This may well reflect the fact that more acutely unwell patients require intensive monitoring and hence a greater number of diagnostic blood tests. However, this in turn puts these already vulnerable patients at greater risk of developing iatrogenic anaemia. There was also a statistically significant negative correlation between haemoglobin concentration on discharge from ICU and the volume of blood taken for analysis (p<0.01). Although this fall in haemoglobin cannot be entirely explained by DBL, it nevertheless emphasises the importance of minimising the frequency of phlebotomy in ICU patients in order to prevent iatrogenic anaemia.

Perhaps unsurprisingly, patients who developed respiratory failure which required ventilatory support whilst in ICU had considerable DBL. This can be explained by the fact that these patients require serial ABGs (in which large volumes of blood are discarded), and once again highlights why there is a need to standardise blood taking from sites like arterial lines. As the majority of patients who developed respiratory distress or required a blood transfusion were admitted to GICU, this would explain why GICU patients had statistically significant greater volumes of blood drawn for diagnostic testing (mean 62.3mL per patient) compared to CICU patients (mean 56.3mL per patient; p<0.01). Finally, there was a correlation between the reason for admission to ICU and higher levels of blood loss for diagnostic testing: sepsis patients had the highest volume of DBL. This may have been due to high volumes of blood being taken for culture, FBC and other diagnostic tests.

*Similarities with other studies*

The mean (SD) volume of blood taken for diagnostic testing was similar to that observed by Thavendiranathan (2005) – 74.6mL DBL (52.1), although this study was examining general medical patients. Both Chant (2006) and Vincent (2002) observed lower mean (SD) volumes in ICU patients – 13.3mL (7.3) and 41.1mL (39.7) respectively. Wisser (2003) found that patients lost a median volume of 200mL of blood over the course of their ICU admission. Koch (2015) showed a higher median loss (332mL) over the course of ICU admissions after cardiac surgery. The median blood loss in our study was 350mL over 4 days. In a similar way to Coene (2014) and Koch (2015), the volume of blood discarded from central lines was high and varied considerably amongst patients.

*Limitations*

It must be noted that while this study has identified some potentially vulnerable patient subsets admitted to ICU, the sample size is small which means that generalising the findings must be done with caution. Moreover, the authors have only used estimates of blood loss for each sample and so must accept that this will inevitably lead to a degree of inaccuracy. Finally, anaemia in critically unwell patients is multifactorial and cannot be solely attributed to DBL. Other important contributing causes include: inflammation, coagulopathy, impaired erythropoiesis, active bleeding and decreased red blood cell life cycle (Hayden et al, 2012).

*Conclusions*

Whilst ICU patients clearly require close monitoring, phlebotomy is a significant contributing factor towards iatrogenic anaemia, and patients experience high volumes of DBL. There were considerable volumes of blood being discarded in the first four days of admission, which in turn emphasises the need to standardise and set guidelines for discarding blood from central and other peripheral lines. Moreover, patients with a higher APACHE II score (and hence more severely unwell), patients who developed respiratory distress requiring ventilatory support and patients who had received a blood transfusion are particularly vulnerable subgroups.

Strategies to consider for reducing blood loss from phlebotomy include point of care testing, reducing the number of unnecessary diagnostic blood tests, the use of paediatric tubes (Foulke and Harlow, 1989), blood conservation devices (Page et al, 2013), use of a ‘closed method’ when drawing blood from arterial lines (Gleason et al, 1992), bundling of scheduled blood sampling and charting of cumulative daily phlebotomy volumes. These strategies, when promoted and enforced by local guidelines and policy, should provide an effective means for reducing iatrogenic anaemia.

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RLM, KF and JU designed the study. MRP collected the data. MRP and JH analysed the data. JH wrote the initial draft of the paper. All authors agreed the final manuscript.

**CONFLICT OF INTEREST**

The authors have no competing interests

**FIGURES (captions)**

*Figure 1. Mean volume (mL) of blood discarded per patient per draw by ICU nursing staff from central or peripheral lines (n=40).*

*Figure 2. Mean volume (mL) of blood taken per patient per day over 4 days. Mean volume for all patients (86.3mL) is shown by the line.*

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