AUDIT ON HAEMOLYSIS AND INTRAGAM®P USE

Final Report

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INTRODUCTION

The development of intravenous immunoglobulin (IVIg) has been a milestone in the history of transfusion medicine. For those patients with an immunodeficiency disease or a condition responsive to immunomodulation the introduction of IVIg has also improved their quality of life.

Despite an overall excellent safety record, IVIg can cause serious complications. Between 2011 and 2014, there have been 315 reports of adverse reactions to fractionated products. Sixty eight per cent of these reactions involved IVIg, (trade named Intragam®P)[1].

One of the well recognised complications is haemolysis due to the presence of anti-A and anti-B within the IVIg. Severity ranges from mild to severe anaemia and renal failure[2] with a documented 3% mortality rate[3].

AIM OF THE AUDIT

The primary aim of this audit was to identify how frequently patients were showing signs of haemolysis following high dose Intragam®P administration.

METHOD

Recipients of Intragam®P at the participating District Health Boards (DHBs) were identified from the New Zealand Blood Service (NZBS) blood management system, eProgesa. High dose new recipients, defined as patients who have not received Intragam®P in the six months prior to the audit period (1 July 2012 – 30 June 2013) and then received a dose of at least 1g/kg over a course of treatment (e.g. 0.5g/kg x 2 doses), were selected.

The audit was retrospective, utilising data from the multi-centre NZBS audit covering the 2012/13 financial year.

Data from ten DHBs (Auckland, Canterbury, Capital & Coast, Counties Manukau, Hawkes Bay, MidCentral, Northland, Southern, Tairawhiti and Waikato) was analysed. These ten DHBs accounted for 79% of all IVIg used in that financial year.

Data collected in the previous NZBS audit report[4] and used to populate this audit included:

- Demographic data: age at initiation or start of audit (whichever is later), gender, weight (current). The NHI was not captured. Instead, each recipient was assigned a unique audit number, thus de-identifying the recipient.
- Hospital and DHB (where given, where initiated, and the DHB of domicile, to provide a correction for referrals).
- Clinical Indication: diagnosis and rationale
- Intragam®P Dose: date of issue, gram/kilogram and frequency
- ABO group
- Evidence Level/Criteria: assessed against NBA qualifying criteria and UK selection criteria
- Qualifying criteria: met or not met
- Review Criteria: completed, not completed or yet to be achieved
- For the five commonest conditions (from the previous NZBS audit), the specific qualifying and review criteria that have been met or not met

Data collected specifically for this audit included:

- Hb prior to commencing Intragam®P
- For the two weeks after commencing Intragam®P:
    - Hb
    - Absolute reticulocyte count
    - DAT
    - Total Bilirubin
    - LDH
    - Haptoglobin
    - CRP

The definition of haemolysis, based on Canadian IVIG Hemolysis Pharmacovigilance Group criteria[5], was:

- onset within 10 days of IVIg administration
- drop in haemoglobin of at least 10g/L
- positive DAT
- evidence of at least two of:
    - increased reticulocyte count (>100 x 10^9/L)
    - increased LDH (>250 IU/L)
    - low haptoglobin (<0.3 g/L)
    - high unconjugated bilirubin (total bilirubin >25 umol/L)
    - haemoglobinuria (not checked)
    - presence of significant spherocytes on a blood film
- Excluding patients with a history or examination consistent with an alternate cause of anaemia

The data was collated in a web-based PostgreSQL database[6] with restricted access, on a secure NZBS webserver. Only the TNS collecting the data and the TMS reviewing and analysing the data have access to any patient identifiers. All identifying data has been removed prior to reporting.

Confirmation that the previous audit, and by inference this extension to it, did not require ethics approval was gained from the Multi-region Ethics Committee as well as agreement to participation form the Hospital Transfusion Committees for the DHBs involved prior to commencement.

RESULTS

180 recipients were reviewed (appendix 1). The average age was 33 years (range: 0-95). 55% were male.

A blood group was known in 153 (85%) of recipients with a typical distribution of blood groups (appendix 2), although only in 80% of recipients was this known prior to infusion. The minimum dose to enter this analysis was 1g/kg. Figure 1 shows the distribution of doses with almost all patients receiving 1 – 2 g/kg. The two patients who received substantially more than 2g/kg received 5.2 and 9.4 g/kg for transplant rejection and ITP respectively.

Figure 2 shows the timing of the patient's blood group with 54% tested for the first time in the week prior to infusion of IntragamP. A mere 6% of patients were tested on the day after their infusion or later. 20% remained untested when checked at the end of 2013, i.e. at least six months after the IVIG dose.

Figure 1: *distribution of dose vs weight with lines showing 1g/kg (dotted) and 2g/kg (solid)*

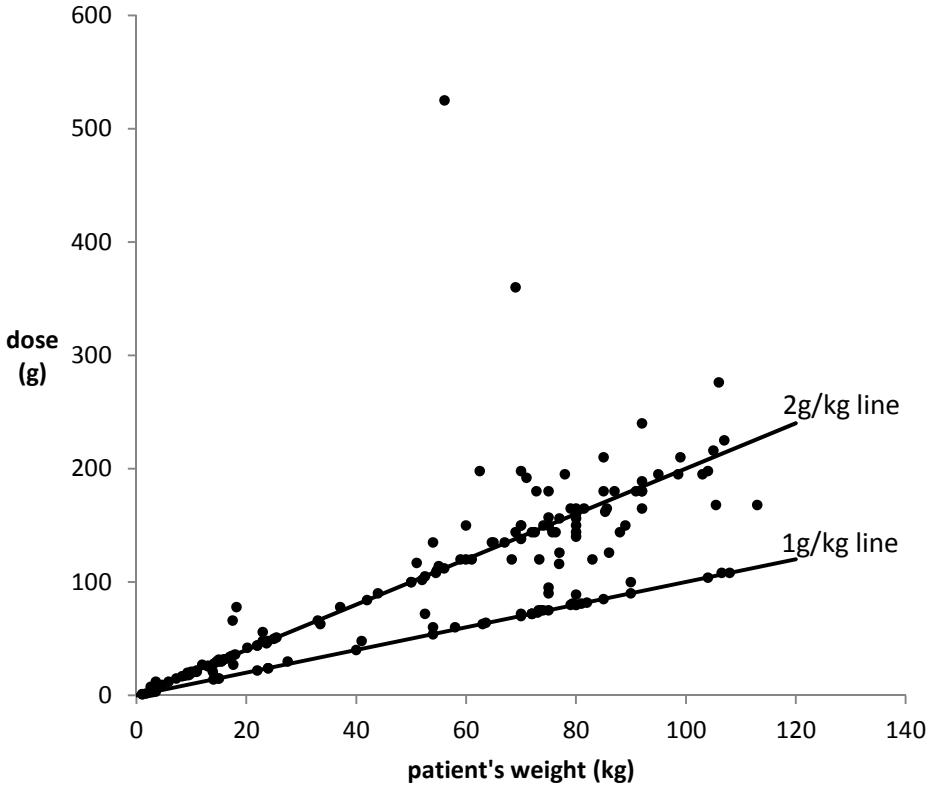
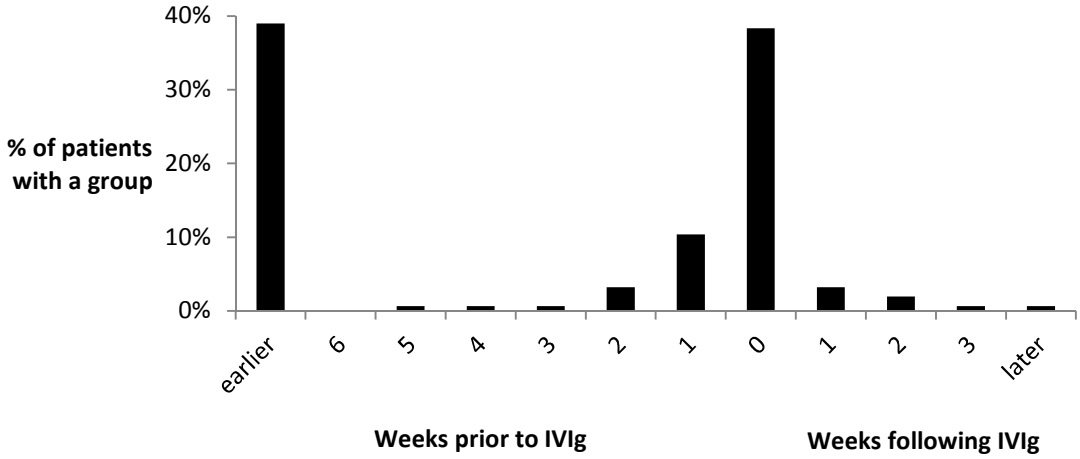


Figure 2: *distribution of timing of blood group testing in IntragamP recipients*



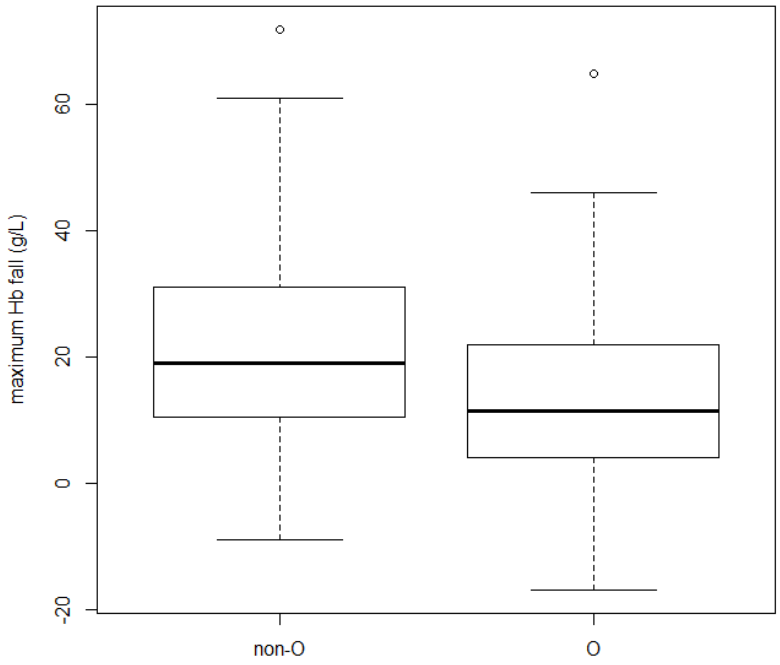
Haemoglobin was checked post-IVIg infusion in 96% of recipients in whom a blood group was known. There was no difference in the proportion of recipients with a haemoglobin result between O and non-O blood group recipients.

Two thirds of patients showed a fall in haemoglobin of at least 10g/L, the qualifying criterion to be considered for IVIg-induced haemolysis (table 1). It is possible that some of this may be due to haemodilution or the anaemia of inflammation associated with the patient's underlying illness. However, when patients with blood group other than group O (non-O) were compared with group O patients, approximately 50% more non-O recipients showed a fall in haemoglobin of at least 10g/L (table 1). If this difference between the two groups is assumed to be entirely due to IVIg, this equates to approximately 22% of all non-O patients.

Table 1: *fall in Hb by blood group and statistical comparison*

Blood group	fall ≥ 10 g/L	no fall or < 10 g/L
AB	5	0
A	39	13
B	11	4
O	27	23
Overall	82 (67%)	40 (33%)
A vs O	75% vs 54%	p=0.0443
A, AB vs O	77% vs 54%	p=0.0199
non-O vs O	76% vs 54%	p=0.0166

Figure 3: *maximum haemoglobin fall vs recipient blood group after IVIG administration*



Looking at the nadir haemoglobin values available for each recipient and comparing the fall with the pre-infusion haemoglobin, showed the average haemoglobin fall in non-O recipients to be significantly greater ($p < 0.05$) (figure 3).

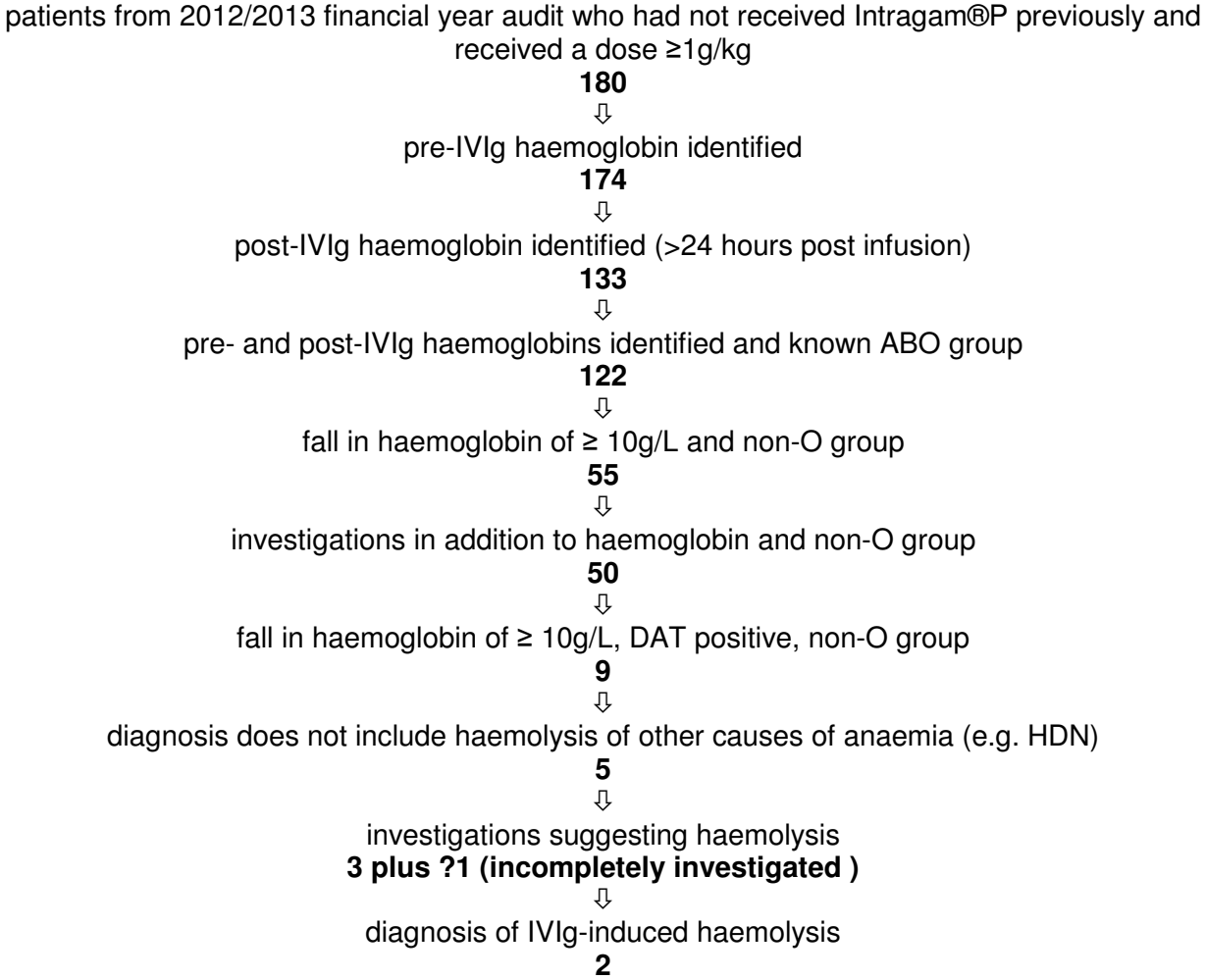
Despite the substantial number of patients showing a fall in Hb, there was no apparent difference in the proportion of patients investigated for markers of haemolysis (table 2). Some of this may be masked by the tests being requested for other indications, as is probably the case for bilirubin. However, it seems less likely there would be other indications for haptoglobin and DAT.

Table 2: *number of patients with known ABO group, investigated by test and degree of fall in Hb*

	DAT	reticulocytes	total bilirubin	LDH	haptoglobin	any marker	n
fall ≥10 group O	3 (11%)	3 (11%)	19 (70%)	2 (7%)	0 (0%)	19 (70%)	27
fall ≥10 non-O	17 (31%)	13 (24%)	47 (85%)	9 (16%)	7 (13%)	50 (91%)	55
fall <10	7 (18%)	6 (15%)	29 (73%)	3 (8%)	2 (5%)	31 (78%)	40
p (fall ≥10 O vs non-O)	0.19	0.41	0.71	0.52	0.16	0.59	

The numbers involved and their progression towards a diagnosis of IVIg-induced haemolysis in this audit are shown in figure 4. Of the eight patients who showed a fall and a positive DAT, four were known to be haemolysing. Two had haemolytic disease of the newborn, one had autoimmune haemolysis and one had drug-induced haemolysis. Of the remaining four, only two had results that would meet the Canadian criteria to be considered for IVIg-induced haemolysis. One patient had Guillain-Barre Syndrome and one had Kawasaki's Disease. Both were diagnosed with IVIg-induced haemolysis.

Figure 4. *Flowchart of patient numbers in relation to IVIg-induced haemolysis*



DISCUSSION

This audit has highlighted several interesting findings:

1. The system (blood banks and clinicians) appears to be well aware of the recommendation for the patient to have a blood group on record prior to administering IVIg. This is apparent from the spike of blood groups taking place on the day of and a few days prior to IVIg administration. This is an improvement on the 2006 audit where 55% recipients with a dose of 1g/kg had a blood group on record prior to infuxion, compared with 80% in this audit.

2. Despite the awareness of a need for a blood group, only two thirds of patients had a package of a blood group, a pre-infusion haemoglobin and a post-infusion haemoglobin. There was no apparent difference in this proportion for O and non-O blood group recipients. This suggests that while the mechanisms for grouping patients may have improved, there is still a significant lack of awareness of the importance of checking for haemolysis in patients receiving high dose (≥1g/kg) IVIg for the first time

3. Although a large percentage of patients were tested for at least one of the markers of haemolysis, the lack of a consistent pattern suggests that few were being investigated in a considered way for haemolysis, despite a fall in haemoglobin of at least 10g/L detected in 55 recipients with known non-ABO group.

4. Comparing O vs non-O blood group recipients, a statistically highly significant difference in the proportion of patients dropping their haemoglobin by at least 10g/L was noted. Extrapolating the data, suggests that 14 cases of unidentified IVIg-induced haemolysis may be present in this data set. This would give an incidence of 13% in patients receiving IVIg at a high dose and for the first time, or 22% if only non-O recipients were considered. This assumes that all cases of IVIg-induced haemolysis are due to anti-A or anti-B and that any pathology causing a fall in haemoglobin is evenly distributed across O and non-O recipients. Haemolysis secondary to IVIg is well described in relation to high dose treatment[3,7–10]. It has also been described in Primary Antibody Deficiency with IVIg given at replacement doses (i.e. 0.4g/kg)[11]. However it is difficult comparing New Zealand rates with those of other countries and different facilities have different regulations around the collection of plasma, In New Zealand, plasma for IVIg is excluded if there is a red cell antibody with a titre ≥ 50. This would prevent some of the cases of haemolysis reported. On the other hand, Intragam®P does not undergo a stage in manufacture to reduce anti-A and anti-B levels as is seen in some products, notably Privigen®[12].

5. Two cases of IVIg-induced haemolysis were identified, giving a raw incidence of 1% in all patients receiving IVIg at a high dose and for the first time, or 2% if only non-O recipients were considered. This rate is similar to that previously published[13].

6. While haemolysis is generally considered an unwanted side effect of IVIg treatment, it is worth noting that anti-D immunoglobulin, when infused to RhD positive recipients for ITP, commonly causes haemolysis[14]. Although the link between the haemolysis and therapeutic response has not been well elucidated, it is possible that the haemolysis may have a beneficial effect in some conditions. However, this remains untested in IVIg and given the seriousness of adverse events associated with anti-D immunoglobulin administration for ITP, close monitoring for haemolysis is required for both products.

CONCLUSION

This audit has identified two cases of IVIg-induced haemolysis but has shown a statistically significant increase in post-IVIg fall in haemoglobin in non-O blood group recipients. Together with the variable investigation of these recipients by their clinicians, this suggests that IVIg-induced haemolysis may be occurring more often than the two cases suggest.

RECOMMENDATIONS

1. Prescribers should have an increased awareness of this issue.
2. Recipients' ABO group should be known prior to infusing IVIG of 1g/kg or more to be able to assess if the recipient is at increased risk of haemolysis.
3. Non-O recipients should have a pre-infusion haemoglobin measurement plus a follow-up haemoglobin measurement within a week of the infusion.
4. If the recipient's haemoglobin falls by ≥ 10 g/L, further investigation of possible haemolysis should be undertaken together with an assessment of possible renal impairment.

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APPENDICES

Appendix 1: *recipient numbers by DHB recipients*

DHB	n
Auckland	44
Canterbury	37
Capital and Coast	26
Counties Manukau	16
MidCentral	10
Northland	7
Southern	13
Waikato	27
Total	180

Appendix 2: *distribution of blood groups in IntragamP recipients*

Group	% (n)
A	42% (64)
B	13% (20)
AB	4% (6)
O	41% (63)

Appendix 3: *diagnoses in DAT positive non-O recipients with Hb fall ≥ 10g/L and whether Hb fall can be attributed to pathology.*

Diagnosis	Hb fall attributable to diagnosis?
Ataxic Guillain–Barré syndrome	No
Kawasaki disease	No
Atypical Kawasaki disease	No
Guillain–Barré syndrome	No
Guillain–Barré syndrome	No
Idiopathic (autoimmune) thrombocytopenia purpura (ITP) in adults	Yes
Haemolytic disease of the newborn	Yes
Drug or ?paraneoplastic induced thrombocytopenia	Yes
Idiopathic (autoimmune) thrombocytopenia purpura (ITP) in adults	Yes