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Revised ASTH Consensus Guidelines for Warfarin Reversal

Warfarin remains the most commonly prescribed anti-coagulant in Australasia despite the recent introduction and funding of new anticoagulants. Warfarin is a coumarin derivative which works by blocking production of the vitamin K dependent coagulation factors (factors II, VII, IX and X). Whilst it has been shown to be effective in the prevention and treatment of a wide range of disorders, warfarin is also associated with a risk of major bleeding (requiring hospitalisation or resulting in death) of 1-3% per year for patients on long term therapy. Due to the risks associated with warfarin anticoagulation, assessment of patients prior to initiation of warfarin, careful management of patients on warfarin, and effective reversal of anticoagulation in the event of bleeding are all essential.

The recent revision of the Australasian consensus guidelines for warfarin reversal⁽¹⁾ include a number of changes from the previous guidelines released in 2004⁽²⁾. These include the use of FFP in warfarin reversal, dosing of Prothrombinex-VF and assessment of thrombotic risk and management of patients around the time of elective surgery.

Principles of initiation

Warfarin associated bleeding risk is highest in the first three months of treatment^(3,4). While a high INR is associated with an increased risk of bleeding, a large proportion of bleeding episodes occur with the INR within the normal range, indicating the influence of patient associated risk factors and the need to consider these both prior to initiation and throughout warfarin treatment. The 2013 consensus guidelines provide a summary of principles to consider for prevention of high INRs, including a recommendation that initial starting doses be 5mg/day, and possibly lower in elderly patients.

Warfarin reversal

The principles of warfarin reversal are to overwhelm the inhibition of vitamin K dependent clotting factor production with vitamin K allowing the body to produce these factors again, and when necessary replacing those clotting factors using plasma derived blood products for immediate correction of the warfarin induced coagulopathy.

The only available vitamin K₁ preparation in New Zealand is Phytomenadione, an intravenous formulation which can also be administered orally. Subcutaneous and intramuscular administration are contraindicated due to variable absorption and the risk of haematoma formation. Both intravenous

and oral routes achieve a similar correction of INR by 24hrs, however the intravenous route achieves a more rapid response with an onset of action seen within 6-8hrs. There has previously been concern surrounding the occurrence of anaphylaxis following intravenous administration. Although no figures are provided, the 2013 guidelines state that the absolute incidence is thought to be very low especially with current formulations.

The immediate replacement of factors II, VII, IX and X can be achieved with either fresh frozen plasma (FFP) or a prothrombin complex concentrate (PCC). The only available PCC in Australasia is Prothrombinex-VF, a 3 factor concentrate containing factors II, IX and X. The 2004 guidelines recommended that Prothrombinex-VF always be supplemented with FFP to provide replacement of factor VII. Since then a number of studies have shown that adequate correction of INR is achieved without the addition of FFP, leading the current guidelines to recommend that Prothrombinex-VF can be used effectively without additional FFP in most clinical situations. Combined use of Prothrombinex-VF and FFP is still recommended in patients with life threatening or critical organ bleeding. This is due to the low number of patients meeting these criteria included in the relevant studies; as such the efficacy of Prothrombinex-VF alone in these situations has not been adequately established.

The 2013 guidelines provide detailed recommendations on warfarin reversal depending on the clinical situation and the INR level. The majority of changes from the previous guideline relate to minor differences in the doses of vitamin K and more detailed recommendations on Prothrombinex-VF dosing. While the 2004 guidelines gave a range of 25-50IU for reversal, the updated guidelines provide a table of dosing recommendations depending on the starting and target INR. The other major difference, as mentioned above, is the removal of the need for use of FFP in addition to Prothrombinex-VF except in patients with life threatening or critical organ bleeding (including intracranial haemorrhage).

Peri-operative management of warfarin anticoagulation

Management of warfarin anticoagulation around the time of surgery requires consideration of the risk of thrombosis if warfarin is withheld, against the bleeding risk associated with the surgery planned. The post-operative thrombotic risk is dependent on both the indication for warfarin and the type of surgery that will be performed.

The 2013 guidelines categorise patients into high,

moderate and low risk of thromboembolism according to their indication for warfarin and other thrombotic risk factors. Strategies for warfarin reversal and post-operative management of anticoagulation depending on the patient's risk group are provided. In addition to the traditional bridging strategy detailed in the 2004 guidelines requiring warfarin to be stopped 5 days pre-operatively the 2013 update provides an alternative option for reversal of high risk patients with a very stable pre-operative INR, in which 3mg of vitamin K is given the day prior to surgery therefore removing the need for bridging anticoagulation. This strategy has been shown to achieve a preoperative INR of <1.5 in 94% of patients with low rates of warfarin resistance when warfarin is restarted.

Summary

The 2013 consensus guidelines for warfarin reversal provide detailed recommendations on the reversal of warfarin in both emergency and elective clinical scenarios. The details of these recommendations can be found within the guidelines. New Zealand Blood Service is developing a range of tools to support their introduction. A smart phone application developed by one of the guidelines authors is already available from the Apple app store (search 'reversing warfarin'). An android version of the app and a pocket guide are also being developed. Consultation with a specialist is recommended if further advice is required regarding emergency or elective reversal of warfarin.

References:

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Evogam - A New Subcutaneous Immunoglobulin Product

Evogam was approved by Medsafe during December 2012. It is a new subcutaneous immunoglobulin product produced by CSL Behring Australia from plasma collected by NZBS. The product is approved for use as an immunoglobulin replacement treatment in patients with primary and secondary immunodeficiency.

Evogam is manufactured using a similar process to that used for Intragam P. It is then formulated as a 16% concentration for use in the subcutaneous setting. New Zealand Immunology departments participated in the clinical trials undertaken by CSL

Behring Australia to gain registration. These patients were successfully transferred from the clinical trial product to the approved version of the product during February this year. NZBS is now increasing production of the product to enable further patients to transition to subcutaneous immunoglobulin treatment over the next few months.

Subcutaneous immunoglobulin replacement therapy allows patients to administer their own treatment at home thus removing the requirement for day case admission for Intragam P infusions. Many patients prefer this approach. It will not however be suitable for every patient and some will choose to remain on the intravenous product.

Information on Evogam for both healthcare professionals and recipients is available on the NZBS website (www.nzblood.co.nz).

A Clinical Audit of Overnight Transfusion in Eight New Zealand Hospitals

Non-essential overnight transfusion interrupts the recipient's sleep and also that of neighbouring patients. Transfusing overnight can also expose the patient to avoidable risk factors such as inadequate observation and monitoring, related to the reduced lighting and lower staffing levels.

This audit reviewed the transfusion of red cell units between the hours of 8pm and 8am at eight large public hospitals in New Zealand over four weeks, excluding high acuity areas (emergency departments, intensive care units, high dependency units, operating theatres, birthing units and delivery suites).

9% (535) of all red cell units transfused at the audited hospitals were transfused overnight in non-high acuity areas. Of the units transfused overnight:

- 66% were for symptomatic anaemia or active bleeding/haemolysis.
- 16% were for asymptomatic anaemia.
- 42% were assessed as not essential for overnight transfusion.
- 49% of post-transfusion haemoglobin levels were greater than 100 g/L, indicating a high degree of liberal transfusion.

Overnight transfusions most frequently commenced before 11 pm, suggesting the drive to transfuse overnight is not a clinical factor, which might be expected to occur more evenly during the night. Only 16% of patients were discharged the following day.

The median time intervals between taking either the pre-transfusion haemoglobin sample or the pretransfusion group and screen sample and commencing the transfusion were 9 hours and 9.2 hours respectively. Based on these findings, overnight transfusions cannot be justified by delays in obtaining the patient's haemoglobin result.

Transfusion practice appeared to be worse at night than during the day. This is suggested by twice the rate of transfusions lasting more than four hours and half the rate of adverse reaction reporting when compared with a previous audit of bedside transfusion practice of the same hospitals, as well as by the fall-off in observations documented over the duration of the transfusion.

This audit has shown a significant reduction in the amount of overnight transfusion when compared to the previous audit undertaken in 2004. Nevertheless a significant proportion of these transfusions appear to have taken place at night because of a systematic failure to commence the transfusion during the day, combined with a liberal transfusion strategy. The poorer compliance to recommended best practice observed during overnight transfusions adds support for further action to reduce this risk to patient safety.

Recommendations arising from the report for DHBs are to:

- re-emphasise policy to restrict overnight transfusion to clinically urgent cases only
- encourage nurses to challenge directives to transfuse stable patients overnight
- improve systems to maximise the opportunity to transfuse during the day
- reinforce a restrictive transfusion strategy to reduce all inappropriate transfusions

NZBS 7th Annual Haemovigilance Report 2011

The annual haemovigilance report was published in November 2012 and includes information and analysis of adverse events and reactions associated with transfusion during 2011. It is available on the NZBS website (www.nzblood.co.nz). Hard copy versions are available from the NZBS National Office (e-mail jillian.sinden@nzblood.co.nz).

Recombinant Factor VIIa – its status in New Zealand in the 2nd decade of the 21st century

Over 20 years ago recombinant factor VIIa (rFVIIa) was developed to treat bleeding in haemophilia patients with inhibitors to factors VIII or IX. What are the antecedents of rFVIIa? Initially, the only treatment available for haemophilia patients who had inhibitors and were bleeding was very large doses of factor VIII or IX. Then, based on what was known about the coagulation cascade, agents that could bypass the steps involving FVIII or IX were considered. Prothrombin complex concentrate (PCC) which contains FVII, in addition to other vitamin K dependent factors, was such a product. FVII was known to convert FX to FXa thus directly acting

on the common pathway and leading to thrombin and fibrin generation. A refinement of this, wherein the factors in PCC were activated, was developed – this was called FEIBA or Factor Eight Inhibitor Bypassing Activity. Ultimately, this led to rFVIIa in the 1980s. Empirically, doses of around 100 mcg/kg were found to be effective. Because rFVIIa, like native FVII, has a short half-life, doses needed to be repeated every 3 – 6 hours. Continuous infusion regimens are also found to be effective.

Though the mode of action is controversial, rFVIIa, like native FVII, works through the extrinsic pathway – the pathway that is likely more important for physiological haemostasis. It does this through both tissue factor (TF)-dependant mechanisms at injury sites and also through TF-independent mechanisms on the surface of activated platelets. Either with, or without TF, rFVIIa essentially acts as a 'tenase' converting FX to FXa.

Initially, rFVIIa was only used in haemophilia patients with bleeding and inhibitors. Later, because of its dramatic effects in these serious conditions, and because of its postulated mechanisms of action, rFVIIa was used to control bleeding in many other conditions. However, licensed indications for rFVIIa are still few. Apart from the haemophilia indication, there are a couple of rare disorders which are also licensed indications – inherited FVII deficiency and Glanzmann's thrombasthenia, a rare platelet function disorder.

Despite this, rFVIIa use for unlicensed indications ('off-licence' or 'off-label' use) overtook the use for licensed indications several years ago. In 2008 these accounted for over 95% of rFVIIa use. Examples of 'off-licence' use include bleeding during cardiac surgery or liver transplantation, after trauma or oral anticoagulants, and for treating intracranial haemorrhage. Often, rFVIIa has been used in a last ditch attempt to control haemorrhage. Importantly in these contexts, rFVIIa, unlike other clotting factors, has been found to be effective even when there was hypothermia. However, like the other factors, rFVIIa is not believed to be effective at low pH. Guidelines for rFVIIa use were developed around the world including New Zealand. Essentially, they advocated that rFVIIa should be tried only after surgical causes of bleeding had been attended to, pH had been corrected, and only if bleeding persisted after the replacement of clotting factors and platelets.

Regional interest in rFVIIa has been considerable. The Australia and New Zealand Haemostasis Registry, established under the auspices of the Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, recently published its final report of 10 years experience in the region with rFVIIa for off licence indications. This encompassed 3440 occasions when it was used in 3314 patients. The main conclusions from this large study are that cardiac surgery, non-cardiac surgery and

trauma were the top three reasons for use; most patients received one dose; the median dose was 91 mcg/kg; bleeding appeared to reduce or stop in about 75% of patients; there was no observable dose-response effect and there was no increase in thromboembolic events.

Earlier this year an analysis of the off-licence use of rFVIIa in Christchurch was undertaken covering the period March 2010 – February 2013. This found that cardiac surgery accounted for 93% of use for off licence indications (28 patients) in contrast to the Australia and New Zealand Registry report where this indication accounted for only 45% of cases. The reason for this difference is not clear. Further analysis was limited to the cardiac surgery cases and this found that the 28 patients had received a total of 32 doses, with a median age of 62 years. 82% were male, 86% of cases where it had been used could be classed as 'complex' cardiac surgery. 82% of doses were to treat bleeding but in 18% of cases it was unclear if this was therapeutic or prophylactic. The median rFVIIa dose was 81.6 mcg/ kg, average blood component use before rFVIIa was given was essentially not significantly different to that in the 24 hours after rFVIIa and 25% suffered an arterial thromboembolic event. Bleeding was recorded as more controlled after rFVIIa in 57% of cases and as continuing in 12.5%.

Interestingly, the analysis found that only 1 patient (4%) had rFVIIa use conforming to institutional guidelines with 50% getting rFVIIa before any RBC transfusion and 7% before any blood components of any sort. In New Zealand a 2 mg vial of rFVIIa costs \$2327.50. The estimated cost of rFVIIa was \$8975.00 per patient with a total cost of \$251,370.00 for these 28 patients. While on the subject of cost, it may be useful to point out that the non-availability of 1 mg vials in New Zealand means that it is harder (than say in Australia where these are available) to match calculated dose with the number of vials required to get that dose. This leads to wastage. The analysis has been discussed with the cardiac surgeons & anaesthetists and it is now planned to collect more data prospectively and re-audit use.

Recent reviews, synthesising results from both observational studies and randomised controlled trials, have failed to show clear evidence of benefit, in any off-licence situation - especially with respect to clinically relevant outcomes such as mortality, length of stay in hospital or blood component usage. On the contrary, more frequent arterial thromboembolic events have been noted. Two other issues also need to be touched on. Firstly, it was never clear what dose of rFVIIa should be used in these off-licence situations. Doses previously found effective in haemophiliacs were used though there are many reports of considerably lower doses also being effective. Secondly, with rFVIIa being the very expensive drug that it is, it has been hard to decide if the costs justify

the benefits and if lowering doses might bring costs down to the point where it might do so.

Thus, while there is little doubt about the licensed indications for rFVIIa, as far as the off-licence uses are concerned, it would appear that initial enthusiasm is being replaced with scepticism. Whether this will again turn to enthusiasm will depend on further information on effectiveness, safety, minimal effective doses and future costs.

Introduction of Rhophylac – A New Rh D Immunoglobulin Product Suitable for Intravenous Use

CSL Behring Australia manufactures an Rh D immunoglobulin for NZBS. This is used to prevent the formation of anti-D in Rh D negative pregnant women. The use of the product has contributed significantly to the reduction in the number of cases of Rh haemolytic disease over the last 50 years. The standard preparation provided by NZBS is suitable for intramuscular injection.

A small number of women have larger foeto-maternal bleeds necessitating larger doses of Rh D Immunoglobulin. Intravenous administration is preferred in these situations. For many years NZBS has provided WinRho, a commercial product, distributed in New Zealand by Baxter Healthcare, for this purpose. Unfortunately they have recently notified NZBS that they will no longer be supplying the product.

Rhophylac is an alternative commercial Rh D Immunoglobulin. Manufactured by CSL Behring from US paid donor plasma, it is suitable for intravenous administration. NZBS will provide Rhophylac for those patients requiring an intravenous product from July 2013.

Rhophylac is currently registered by the United States Food and Drug Administration (US FDA) and by the Australian Therapeutic Goods Administration (TGA). It has not been submitted for evaluation to Medsafe and therefore will be provided as an authorised medicine on a section 29 basis. This is the same mechanism that was used to distribute WinRho.

Rhophylac is only available in a 1500IU dose size. This is significantly larger than the standard Rh D Immunoglobulin provided by NZBS (625IU) and WinRho (600IU). Care will be required to ensure that patients receive the appropriate dose of the product. In order to assure this, all issues of Rhophylac will require approval by one of the NZBS Medical team. This will not delay access to the product which will continue to be available from larger Blood Banks across the country.