REVIEW ARTICLE

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An Evaluation of Eptacog Alfa in Nonhaemophiliac Conditions

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Abstract

We have analysed the published literature on eptacog alfa (recombinant factor VIIa; rFVIIa) for nonhaemophiliac conditions with the aim of determining its current place in therapy.

Initial surgical and/or medical management is required for any patient with life-threatening bleeding. In those with continued life-threatening bleeding (i.e. despite maximal surgical and/or medical therapy), eptacog alfa may be considered as additional therapy, in exceptional circumstances. There is good evidence from systematic reviews and randomized controlled trials (RCTs) that eptacog alfa stops bleeding in adults with intracerebral haemorrhage (ICH) if it is given within 4 hours of symptom onset. However, a recent phase III RCT suggests that it does not improve clinically relevant long-term outcomes (death and disability). There is also good evidence against prophylactic use of eptacog alfa during orthotopic liver transplantation or liver resection, and in treating variceal and nonvariceal haemorrhage in patients with cirrhosis. The evidence for the use of eptacog alfa for unexpected life-threatening bleeding in liver, cardiac or other surgery, or in blunt trauma, is not robust. In these circumstances, it should only be given as part of a clinical trial or in exceptional cases when other therapies have failed. The evidence for use of eptacog alfa in penetrating trauma is lacking. Conflicting RCT results exist for the prophylactic use of eptacog alfa in elective surgery; therefore, it cannot be recommended in this situation. There is insufficient evidence for a primary role of eptacog alfa in reversal of anticoagulation with heparin-like molecules and novel anticoagulant agents. There are effective therapies that

correct all warfarin-induced factor deficiencies; thus, off-label use of eptacog alfa for reversal of warfarin should only be considered in the context of ICH.

The evidence for eptacog alfa use in children is limited. The only RCT is in cardiac surgery for congenital heart disease, where eptacog alfa prophylaxis was actually associated with increased time to chest closure. It may be of potential benefit in some children with life-threatening bleeding in the context of trauma, surgery or liver disease (as additional therapy when surgical and/or medical control of bleeding has failed), but the overall benefit-risk ratio may be unfavourable if there is an underlying risk of thromboembolism (e.g. trauma, congenital heart disease, other hyperviscous or hypercoagulable states, presence of arterial or central venous catheters).

Thromboembolism may be associated with eptacog alfa use. Although the magnitude of this risk and possible predisposing factors are not clearly delineated, some data suggest increased risk at higher doses. Variable effects of eptacog alfa use on mortality have been shown in a pooled analysis of RCTs. Data from some observational studies and postmarketing surveillance suggest an increased risk of thromboembolism associated with off-label uses. Further well designed studies are required to more definitively assess the risk of thromboembolism with eptacog alfa and to better determine its effects on mortality.

Optimum dosages for nonhaemophiliac conditions are not defined and nor is the optimum timing of administration. Moreover, it is not clear which patients will be most likely to benefit in terms of haemostatic efficacy and mortality. In addition to conventional measures to stop bleeding (i.e. surgery and blood transfusion), correction of hypothermia and acidosis, and reversal of anticoagulation are all recommended. The outcomes (effectiveness and safety) of all off-label uses should be systematically evaluated and reported. Adequate data to assess cost effectiveness for eptacog alfa does not exist for most off-label indications.

Haemostasis *in vivo* is predominantly directed by the tissue factor/factor VIIa (FVIIa) pathway. FVIIa in combination with tissue factor exposed at sites of tissue injury activates plasma factor X and drives thrombin generation. Thrombin is the key enzyme that converts fibrinogen to fibrin, activates platelets and forms a stable haemostatic plug. Recombinant FVIIa (rFVIIa, eptacog alfa activated, NovoSeven® [1]) is a new therapeutic agent administered by intravenous injection with identical activity to native FVIIa. This agent has revolutionized the management of bleeding in patients with congenital or acquired haemophilia and inhibiting antibodies toward factor VIII or IX. This is the current registered indication in most countries for use of this agent. The potential of this haemostatic agent to control serious bleeding in nonhaemophiliac patients has been reported. Increasingly, eptacog alfa is being prescribed for a variety of 'off-label' indications and it has orphan status or licensing for some of these (e.g. for the prevention and treatment of bleeding episodes in patients with congenital FVII deficiency, Glanzmann's thromboasthenia and post partum haemorrhage in patients unresponsive to standard obstetric management). The purpose of this review is to collate all of the available evidence on the efficacy and safety of eptacog alfa in other 'off-label' conditions in order to facilitate overall benefit-risk assessments when making decisions about the appropriateness of use in a variety of clinical

1 The use of trade names is for identification purposes only and does not imply endorsement.

contexts. Such collated information (especially with comprehensive safety data) is usually not available from a single source for most off-label uses. This review aims to provide more accessible comprehensive information about benefits and risks to help determine the current place in therapy for eptacog alfa in nonhaemophiliac conditions.[1]

1. Methodology

A focused search of EMBASE (January 2002 to February 2008) using the MESH terms 'blood clotting factor 7' or 'blood clotting factor 7a' or 'recombinant blood clotting factor 7a' was performed (limited to human studies and 'treatment' with two or more terms, high sensitivity and articles or reviews). The same search was performed limited to case control studies/cohort analyses to capture relevant studies reporting lower frequency outcomes relevant to the safety assessment. All of the results were assessed and the selected papers are presented in this article. A similar MEDLINE search was also performed. Online searches of best evidence websites were also performed: useful material was obtained from the Cochrane Collaboration, Canadian Agency for Drugs and Technologies in Health (CADTH) and Medscape and from the US FDA. NovoNordisk (Australia) was approached for any further data, especially relating to safety outcomes.

This review presents a systematic collation of the available evidence about the efficacy and safety profile of eptacog alfa in nonhaemophiliac conditions, synthesized according to levels of evidence and grades developed by the Australian National Health and Medical Research Council pilot program (2005–7).[2] It is not a systematic review (in its strict definition) or the consensus of key opinion leaders. We did not co-select and evaluate papers initially; rather, one author performed the initial search and selected papers. Additional papers were included, according to relevancy, as writing/editing progressed. Results of other systematic reviews were included because they formed the basis of our grading system where, together with randomized controlled trials (RCTs), they are regarded as the best evidence. We also included a substantial safety section in order to reduce the efficacy bias seen in most reviews. The best evidence for or against the use of eptacog alfa came from systematic reviews of RCTs or from well designed RCTs. The date of publication of the systematic reviews was factored into our determination of place in therapy: i.e. in general, the most recent reviews should be of greatest value. All of the reviews were included because they form part of the evidence to determine place in therapy. Less robust evidence about efficacy consisted of only nonrandomized or other similar studies showing some consistency of benefit (or from less convincing or conflicting results from RCTs). The lowest level of evidence for efficacy consisted of case studies, case series or other studies with high risk of bias. It is important to note that this evidence and the grading system is very much efficacy focused. The types of studies needed to enable more comprehensive evaluation of safety include observational studies (e.g. cohort studies, case control studies, registries) and data from postmarketing surveillance (e.g. spontaneous reports).[1] Information about uncommon or rare but serious adverse effects that are not detected in RCTs may only be obtained from such sources. Thus, safety data from a range of sources are summarized in section 10 of this article, which is a unique aspect of our review. In sections 3–10, all of the available RCTs were included; however, other studies were selected to show the quality of other evidence for each condition.

2. Search Results and Analysis

2.1 Overall Results

Table I lists the indications that were analysed for evidence and shows the current place in therapy based on the quality and extent of that evidence. Sections 2.1–2.3 summarize findings from systematic reviews and registries, while sections 3–9 provide specific evidence for each condition as well as a separate paediatric section. Overall, the evidence base for the use of eptacog alfa in nonhaemophiliac conditions is scant, and more RCTs are required to solve numerous questions ranging from haemostatic efficacy and safety outcomes to appropriate dose

Table I. Place in therapy of eptacog alfa (recombinant factor VIIa) in nonhaemophiliac conditions (refers to adult patients only, apart from specific paediatric section)

Indication	Evidence[a]	Place of eptacog alfa in therapy
Intracerebral haemorrhage	B	There is evidence that it may stop bleeding if given within 4 hours of symptom onset. May not improve outcomes; however, recent data suggest patients <75 years of age may benefit more than older patients. Use only where standard therapy is not a reasonable option and as part of a clinical trial
Liver disease	B	Should not be used for variceal and nonvariceal haemorrhage in patients with cirrhosis
Liver surgery	B	Prophylactic administration is not effective during orthotopic liver transplantation or liver resection
Blunt trauma	C	May be used in patients with life-threatening bleeding
Cardiac surgery	C	May be used in patients with life-threatening bleeding.[b] May reduce need for transfusion when given after cardiac bypass to prevent bleeding
Liver surgery	C	May be used in patients with life-threatening bleeding[b]
Other surgery	C	May be used in patients with life-threatening bleeding[b]
Reversal of warfarin therapy	C	Effective therapies that correct all warfarin-induced factor deficiencies are available; thus, it should be considered only in the context of intracerebral haemorrhage
Other surgery	D	Should not be used prophylactically in elective surgery
Penetrating trauma	D	Surgical control of massive haemorrhage is first-line management as eptacog alfa appears less effective when very high transfusion rates are required. May be used in patients with life-threatening bleeding[b]
Reversal of other anticoagulants	D	There is insufficient evidence for a primary role in reversal of anticoagulation with heparin-like molecules and novel anticoagulant agents
Paediatrics	D	Evidence is very limited. May be used for life-threatening bleeding in the context of trauma, surgery, liver disease and prematurity, but need to weigh against increased thromboembolic risk in some of these patient groups[b]

a Based on Australian National Health and Medical Research Council grading: B = good evidence from systematic reviews and/or RCTs for or against its use (an A grading would signify a greater extent of this type of data); C = less robust evidence or conflicting results from RCTs, or data from nonrandomized or other studies, for or against its use; D = poor evidence from RCTs or other studies or from case studies/series for or against its use. Refer to individual sections of this article for details of available evidence.

b Use only as additional therapy where there is continuing life-threatening bleeding despite maximum surgical and/or medical therapy. It should be noted that the overall benefit-risk ratio may be unfavourable if there is an underlying risk of thromboembolism (e.g. trauma, hyperviscous or hypercoagulable states, or presence of arterial or central venous catheters).

RCT = randomized controlled trial.

and timing of administration. Therefore, for indications other than intracerebral haemorrhage (ICH) in adults (see table I), it is recommended that off-label eptacog alfa use ideally should occur only as part of a clinical trial or be reserved for use in 'exceptional' circumstances as defined by predetermined criteria.[1] These would include (i) clear definition of what is considered standard therapy (e.g. guidance on the standardization of medical management of massive haemorrhage, prior to consideration of eptacog alfa as additional therapy [see section 14]); (ii) evaluation and approval of use by an institutional drug committee or its delegate; (iii) informed consent (where possible, within constraints of clinical context); and (iv) assessment and reporting of outcomes to add to the body of knowledge about off-label uses.

2.2 Summary of Systematic Reviews and Consensus Guidelines

The most recent systematic review was published by the Cochrane Collaboration.[3] They included 13 RCTs in their evaluation (all of these are included in this review) – six involving prophylactic use of eptacog alfa (724 patients) and seven of therapeutic use in 1214 patients. Pooled results from the prophylactic studies showed no significant advantage (or disadvantage in the case of adverse events) of eptacog alfa over placebo; however, the authors stated there was a trend towards reduced transfusion requirements with eptacog alfa compared with pla-

cebo but an increased trend in thromboembolic adverse events. Similarly, no significant advantage or disadvantage was found from pooled results of the therapeutic trials, but a trend for reduced mortality and increased risk of thromboembolic adverse events with eptacog alfa was found. However, it should be noted that they did not include the RCTs in ICH in their pooled results because of methodological differences from the other studies: these studies did show a positive result for eptacog alfa use in ICH. The authors concluded that the use of eptacog alfa either prophylactically or therapeutically in nonhaemophiliac patients remains uncertain. They stated that results were more positive for therapeutic than prophylactic use of eptacog alfa and that future research should give priority towards therapeutic use, with mortality as a primary outcome; or, if blood loss/transfusion requirements are being measured, that trials should be adequately powered (i.e. the magnitude of eptacog alfa treatment effect has been smaller than hoped for in published trials).

The conclusion of a systematic review of studies up to July 2004 was that eptacog alfa showed promise as a prohaemostatic agent in nonhaemophiliac patients who experience major bleeding.[4] The authors recommended that off-label use may be considered in patients with life-threatening bleeding, but that more RCTs are required to assess its efficacy and safety.

A US consensus panel made recommendations based on grading of published evidence (data up to June 2004) and use of eptacog alfa in different clinical scenarios.[5] In summary, eptacog alfa in nonhaemophiliac conditions was deemed appropriate for:

- cardiac, thoracic aortic or spinal surgery, hepatic resection, hysterectomy, or *post partum* bleeding (when significant clotting factor replacement had failed);
- severe multiple trauma (only if surgery and substantial blood replacement were unsuccessful);
- nontraumatic intracranial bleeding (only if <4 hours has elapsed since symptom onset or if traumatic bleeding was associated with anticoagulant use and haematoma expansion).

The CADTH published a review of 11 double-blind RCTs of eptacog alfa in nonhaemophiliac conditions.[6] All of these studies are reported in this review. From all of the studies, there were two significant results for eptacog alfa compared with placebo:

- eptacog alfa showed a significant reduction in mortality among patients with ICH.[7]
- eptacog alfa reduced the number of trauma patients needing massive blood transfusion.[8]

The authors stated there was a nonsignificant trend towards increased mortality and thromboembolic serious adverse events in some trials (e.g. liver transplant, upper gastrointestinal bleeding, stem cell transplantation), and suggested that the efficacy and safety of eptacog alfa in nonhaemophiliac conditions will only become clear after adequately powered phase III trials are published, and that implementation also requires more evidence on its benefit/harm, optimum dose, time of administration and cost effectiveness.

European consensus guidelines based on a systematic review of literature published up until July 2005 were published, which stated that eptacog alfa may be used to treat massive bleeding in certain indications, but only in addition to the surgical control of bleeding once conventional therapies have failed.[9] The authors used best evidence to make graded recommendations and stated that the following conditions may be treated with eptacog alfa:

- control of bleeding in blunt trauma (supported by one large RCT);
- bleeding following cardiac surgery (supported by at least one nonrandomized study);
- *post partum* haemorrhage (supported by sufficient case series, uncontrolled studies and expert opinion);
- uncontrolled bleeding in surgical patients (supported by sufficient case series, uncontrolled studies and expert opinion).

It was not recommended for use in the management of massive haemorrhage associated with penetrating trauma, elective surgery, liver surgery, or bleeding due to Child-Pugh A, B or C cirrhosis.

2.3 Clinical Experience and Registry Information

There is a lack of evidence-based international and national guidelines for the off-label use of eptacog alfa, which has prompted the development of guidelines by multidisciplinary working groups based on clinical experience with the drug. In one US institution, guidelines were implemented as a result of evaluation of medication use.[10] They produced guidelines for use of eptacog alfa in reversal of warfarin toxicity, liver disease, ICH and in paediatrics. Similarly, a multidisciplinary task force in Israel produced guidelines for the use of eptacog alfa in uncontrolled bleeding.[11]

2.3.1 Registry Information

Registries for eptacog alfa use in off-label conditions provide information to complement data obtained from RCTs and other published and unpublished sources of evidence. Although the quality of data obtained from registries can be highly variable, with a number of well recognized potential biases,[12] they can often provide useful information on safety outcomes that are not otherwise available, especially about outcomes of use in larger numbers of more heterogeneous patients than are usually included in RCTs. Voluntary submission of cases for some registries makes them subject to more bias. This review presents results from the Haemostasis Registry, which consists of mandatory reporting of all cases receiving eptacog alfa in participating institutions.[13] An initial report of 40 patients from another NovoNordisk-sponsored database on extended-use eptacog alfa showed some efficacy in stopping bleeding and reducing blood product use.[14] Twenty three of 40 patients died (16 nonbleeding deaths). A further selective analysis of this registry of 45 surgical and trauma patients (February 1999 to February 2004) suggested that eptacog alfa may reduce mortality rate in trauma patients, but this was not observed among the small cohort of surgical patients.[15] A review of 24 cases submitted to the same database suggests that eptacog alfa is beneficial in the management of haemorrhage in patients with thrombocytopenia and haematological malignancies.[16]

3. Liver Disease

3.1 Reviews

In one systematic review, eptacog alfa was not recommended for use in bleeding due to Child-Pugh A, B or C cirrhosis.[9]

3.2 Randomized Controlled Trials (RCTs)

The efficacy and safety of eptacog alfa in 245 cirrhotic patients with variceal and nonvariceal upper gastrointestinal tract bleeding was investigated in an RCT.[17] Patients received eight doses of eptacog alfa 100 μg/kg or placebo (as well as other pharmacological and endoscopic treatment). There was no advantage of eptacog alfa over standard treatment on the primary composite endpoint (failure to control bleeding within 24 hours after first dose, or failure to prevent rebleeding between 24 hours and day 5, or death within 5 days) and no significant differences were observed in mortality. However, subgroup analysis of Child-Pugh B and C cirrhotic patients showed that administration of eptacog alfa may decrease the proportion of patients in whom variceal bleeding is not controlled.

3.3 Other Studies and Cases

There is one dose-escalation study of eptacog alfa in Child's B and C cirrhotic, nonbleeding patients with advanced liver disease.[18] Ten patients with abnormal prothrombin time (PT) values were given three successive dosages of eptacog alfa (5, 20 and 80 μg/kg) over a 3-week period (the authors stated that cirrhotic patients with prolonged PT are known to have low FVII levels). The mean PT was transiently corrected to normal in all three dose groups. A retrospective analysis of 55 patients who received eptacog alfa at one institution looked at mortality and outcome.[19] Underlying liver disease with coagulopathy was the reason for giving eptacog alfa in 26 of the patients. Administration of eptacog alfa corrected laboratory parameters of coagulopathy, but did not alter outcome, and 26 patients died during the same admission from their underlying diseases.

The remaining articles are all case series or case studies. For example, in one series of 112 patients with cirrhosis and an episode of acute upper gastrointestinal bleeding there were eight patients who experienced haemorrhage unresponsive to standard treatments. Administration of eptacog alfa (4.8 mg single intravenous dose) achieved haemostasis in all patients.[20] There is a report of four patients with advanced cirrhosis and severe coagulopathy who underwent polypectomies by snare cautery after an intravenous bolus infusion of eptacog alfa 120 μg/kg.[21] The immediate use of eptacog alfa reduced resource utilization and enabled polypectomies at the initial colonoscopy. No post-polypectomy bleeding was noted.

4. Liver Surgery

4.1 Reviews

A literature review in major abdominal and liver transplantation surgery (details of search not given) concluded that there is no evidence to support extensive use of eptacog alfa in liver transplantation; however, it may be effective as a rescue therapy in extremely severe situations.[22] In one systematic review, eptacog alfa was recommended in hepatic resection or orthotopic liver transplantation (OLT) when significant clotting factor replacement had failed,[5] while in another it was not recommended for prophylactic use in liver surgery but could be used in surgical bleeding if conventional measures had failed.[9]

4.2 RCTs

There are two RCTs of the prophylactic use of eptacog alfa in cirrhotic patients (Child-Pugh class B or C) undergoing OLT.[23,24] In one study, 82 patients were randomized to receive a single dose of eptacog alfa (20, 40 or 80 μg/kg) or placebo administered immediately before surgery.[24] There were no significant differences in the primary endpoint (number of red blood cell [RBC] units transfused during the perioperative period; i.e. surgical time and 24 hours post-surgery) compared with placebo, and the number of adverse events was comparable among the groups. The authors suggested that the doses used might be too low. In a subsequent study in 183 patients, higher eptacog alfa doses (60 and 120 μg/kg) or placebo were repeated every 2 hours perioperatively.[23] However, this study also showed no significant effect of eptacog alfa over placebo on the number of RBC units transfused (primary endpoint, 15% and 23% respective reductions compared with placebo) or intraoperative blood loss. A greater number of patients who received eptacog alfa avoided RBC transfusion (8.3% placebo vs 0% eptacog alfa; $p = 0.03$). There were no group differences in rates of thromboembolic events or hospitalizations, total surgery time and the proportion of patients undergoing retransplantation.

An RCT in 204 noncirrhotic patients undergoing liver resection showed that eptacog alfa (20 or 80 μg/kg, 5 minutes before the first skin cut) produced no significant reduction in the number of patients requiring RBC transfusion during surgery or within 48 hours of surgery (primary endpoint).[25] The authors suggested the number of patients in the study was too small to detect a significant difference. The use of eptacog alfa (50 or 100 μg/kg) or placebo was investigated in 234 cirrhotic patients undergoing liver resection.[26] Active drug or placebo was given 10 minutes before the first skin cut and every 2 hours during surgery. Blood loss was used as a transfusion trigger and the requirement for RBC transfusion was the primary endpoint. There was no statistical difference between the groups.

4.3 Other Studies and Cases

A retrospective study found that prophylactic eptacog alfa (58 ± 18 μg/kg) reduced transfusion requirements in 11 OLT patients and significantly prolonged PT.[27] In a report of four cases of fulminant hepatic failure undergoing urgent OLT, the prolonged PT was corrected by eptacog alfa (90 μg/kg before and during surgery) in all patients; however, thrombotic complications occurred in two patients (myocardial ischaemia, portal vein thrombosis).[28] Eptacog alfa (60–90 μg/kg) was administered to seven patients undergoing OLT, six of whom experienced persistent severe bleeding and

were given eptacog alfa (after conventional measures had failed to stop bleeding) during surgery.[29] In all patients, eptacog alfa allowed sufficient haemostasis to carry on definitive treatment and there were no deaths.

5. Surgery and Trauma

5.1 Cardiac Surgery

5.1.1 Reviews

There is a recent systematic review that looked specifically at the usefulness of eptacog alfa for intractable bleeding after cardiac surgery.[30] Ten studies were found (over the period 2000–6), nine of which were uncontrolled studies in small numbers of patients (range 5–51 patients). The only RCT was for prophylactic use (see section 5.1.2). The authors summarized the results of all studies and stated that eptacog alfa (60–90 μg/kg) produced consistent reductions in blood loss and use of blood products. They recommend its use. A more recent systematic review in cardiac surgery concluded that clear evidence from RCTs is lacking and requires much more research.[31] More general systematic reviews agreed that eptacog alfa was appropriate after significant clotting factor replacement had failed.[5,9]

5.1.2 RCTs

In a pilot RCT, eptacog alfa was given after cardiopulmonary bypass to prevent bleeding.[32] Twenty patients received eptacog alfa (90 μg/kg) or placebo after cardiopulmonary bypass and reversal of heparin. The study was underpowered but the authors stated that eptacog alfa significantly reduced the need for allogeneic transfusion (primary endpoint; two eptacog alfa recipients received 13 units of blood in total while eight placebo recipients required 105 units). Another small RCT (published in Chinese – abstract only received) evaluated the effect of eptacog alfa (40 μg/kg) versus placebo on the early recovery of 22 patients undergoing cardiac valve replacement under cardiopulmonary bypass.[33] The eptacog alfa group received the drug after protamine reversal of heparin. Patients who received eptacog alfa improved their coagulation function and received less blood transfusion compared with placebo.

5.1.3 Other Studies and Cases

Numerous studies and cases of eptacog alfa for uncontrolled bleeding following cardiac surgery were included in the Tanos and Dunning[30] mentioned in section 5.1.1. In addition, a more recent retrospective review showed that eptacog alfa (100 μg/kg), given after failed conventional therapy, reduced the need for blood products.[34]Another retrospective review found that ten patients responded to eptacog alfa (median dose 85 μg/kg); however, mortality was high when eptacog alfa was used after >24 hours and continued bleeding in six episodes necessitated return to theatre where a surgical source of bleeding was found.[35] Successful cessation of bleeding was achieved in seven cardiac surgery patients with intractable bleeding and four of these received low eptacog alfa doses (26–40 μg/kg).[36] In a similar group of 15 patients, low-dose eptacog alfa (1.2 mg as a slow intravenous bolus at the end of complete step-by-step transfusion protocol) was shown to reduce blood loss compared with an earlier group of matching patients who did not receive eptacog alfa.[37] Most recently, a matched-control study of 23 patients undergoing aortic dissection surgery showed that eptacog alfa (70 μg/kg) was a successful additional therapy in patients refractory to conventional methods.[38]

5.2 Other Surgery

5.2.1 Reviews

No review articles specific to surgical patients were found. More general systematic reviews stated that eptacog alfa was appropriate in spinal surgery and in hysterectomy when significant clotting factor replacement had failed,[5] but it was not recommended for use in the management of massive haemorrhage associated with elective surgery.[9]

5.2.2 RCTs

There are no RCTs of eptacog alfa for uncontrolled bleeding in surgical patients, but there are two RCTs of its prophylactic use. In one study, 48 patients with normal haemostasis undergoing

major pelvic-acetabular surgery were given eptacog alfa (90 μg/kg as an intravenous bolus) or placebo when the first skin incision was made.[39] The total volume of perioperative blood loss (primary outcome variable) was not significantly different between the groups and there were no differences in transfusion requirements (secondary outcome). The authors concluded that eptacog alfa does not decrease the volume of perioperative blood loss in patients undergoing this procedure. In the second study, perioperative blood loss up to 24 hours after surgery and transfusion requirements (primary outcomes) in 36 patients undergoing retropubic prostatectomy were assessed following eptacog alfa (20 μg/kg or 40 μg/kg intravenous bolus) or placebo during the operation.[40] Median perioperative blood loss was significantly less in the treatment groups compared with the placebo group ($p = 0.001$). Seven of 12 placebo-treated patients required transfusion but only three who received eptacog alfa 20 μg/kg and none who received 40 μg/kg required this. The authors concluded that eptacog alfa reduced perioperative blood loss and eliminated the need for transfusion in patients undergoing major surgery. Vincent et al.[9] suggested that the reason for the opposing results in these two studies may be due to patient age and type/location of the surgery. Also, the eptacog alfa was administered later in the second study than in the first, which may have affected drug activity.

5.2.3 Other Studies and Cases

Vincent et al.[9] reviewed case studies showing that eptacog alfa was effective at stopping bleeding in surgical patients. More recently, in a retrospective review of 18 surgical or trauma patients who received eptacog alfa (mean dose 100 μg/kg) for coagulopathic bleeding, all but one patient had resolution of bleeding, and transfusion requirements for RBCs and plasma were substantially reduced after eptacog alfa.[41] Another retrospective report looked at the use of eptacog alfa in 40 consecutive patients, 21 of whom were surgical bleeding patients.[42] Results were presented for 31 patients: 21 (68%) showed a reduction or cessation in bleeding (median surgical dose 78 μg/kg). Of 973 patients in one institution who underwent complex vascular surgery, there were 18 patients with intractable bleeding who were given eptacog alfa (40–80 μg/kg) following failure with conventional measures.[43] Twelve of 18 patients responded and survived the operation, while six died. The authors stated that eptacog alfa should be administered early with measures to achieve haemodynamic stability and correction of acidosis.

5.3 Trauma

5.3.1 Reviews

A recent review identified 126 eptacog alfa-treated trauma patients reported in 15 publications up to November 2004.[44] Age range was from 20 months to 88 years and almost 70% had blunt injury. In most patients, eptacog alfa was used after conventional methods had failed. Doses of eptacog alfa varied from 36 to 178 μg/kg, and single and multiple doses (range 2–12 hours) were used. The effectiveness of eptacog alfa (determined by reduction in blood loss, transfusion requirements and mortality) was reported in 80% of patients, and shortening or normalization of coagulation parameters was also shown in most. Thus, the data seemed to support eptacog alfa as an additional therapy for the reduction of haemorrhage and transfusion requirements in trauma patients.

In a review of clinical experience with eptacog alfa in trauma, the authors stated their results have led to guidelines where eptacog alfa (90 μg/kg) is recommended in trauma patients if uncontrolled bleeding continues after conventional therapy.[45] Similar guidelines have also been developed by the Israeli Multidisciplinary rFVIIa Task Force, based on a literature review and the outcomes of the first 36 patients from a prospective registry who received eptacog alfa for uncontrolled bleeding as a result of trauma (blunt, penetrating and blast incidents) in Israel.[11] An initial dose of 120 μg/kg was advised by the authors. A report of battlefield experience with eptacog alfa and other haemostatic agents states that eptacog alfa can stop some cases of severe bleeding due to coagulopathy in military situations.[46]

There are three systematic reviews, which base their recommendations on the RCT by Boffard et al.[8] (see section 5.3.2). The CADTH commented that eptacog alfa reduced the number of trauma patients needing massive blood transfusion,[6] and Shander et al.[5] recommended eptacog alfa for severe multiple trauma if surgery and substantial blood replacement were unsuccessful. Vincent et al.[9] approved its use in blunt trauma but not in penetrating trauma.

5.3.2 RCTs

Two multicentre phase II RCTs were conducted simultaneously to evaluate the efficacy and safety of eptacog alfa in patients with severe blunt and/or penetrating trauma.[8] Selected patients who had received 6 units of RBCs within 4 hours of hospital admission were randomized to receive three injections of eptacog alfa (200 μg/kg followed by 100 μg/kg and 100 μg/kg, 1 hour and 3 hours after the first dose) or three similarly timed placebo injections, immediately after the eighth transfusion of RBCs. The primary efficacy endpoint was the number of RBCs transfused in the 48-hour period following the first drug dose. However, the authors excluded patients who did not survive the 4-hour period and determined that, in blunt trauma, RBC transfusion was significantly reduced with eptacog alfa relative to placebo (estimated reduction of 2.6 RBC units; $p = 0.02$) and the need for massive transfusion (>20 units of RBCs) was reduced (14% vs 33% of patients; $p = 0.03$). In penetrating trauma, similar analyses showed trends towards eptacog alfa reducing RBC transfusion (estimated reduction of 1.0 RBC units; $p = 0.10$) and massive transfusion (7% vs 19%; $p = 0.08$). Trends towards a reduction in mortality and critical complications were observed. The authors concluded that eptacog alfa resulted in a significant reduction in RBC transfusion in severe blunt trauma with only similar trends observed in penetrating trauma. The exclusion of patients from the analysis has been criticised and defended in accompanying letters.[47]

Recently, a pilot study in 18 burns patients undergoing excision and skin grafting showed that eptacog alfa (40 μg/kg administered at first skin incision and 90 minutes later) decreased blood transfusion requirements compared with placebo.[48]

5.3.3 Other Studies and Cases

A retrospective cohort study was conducted among 242 trauma patients requiring transfusion of ≥8 units of packed RBCs within the first 12 hours of admission.[49] There were 38 patients who received eptacog alfa and it was associated with improved 24-hour survival (adjusting for baseline demographics and injury factors). Also, there was a strong trend towards increased overall in-hospital survival. Subgroup analysis showed that 24-hour survivors required a slower initial rate of RBC transfusion, had higher platelet counts and smaller base deficits compared with eptacog alfa recipients who died during the first 24 hours. The authors said that eptacog alfa may be able to improve the early survival of massively bleeding trauma patients but they stated that surgical control of massive haemorrhage was still first-line therapy, as eptacog alfa seemed to be less effective when very high RBC transfusion rates were required. Correction of acidosis and thrombocytopenia may also be key factors in determining eptacog alfa efficacy. In a more recent retrospective study of trauma patients requiring massive transfusion, early administration (i.e. before 8 RBC units had been given) of eptacog alfa to 17 patients led to a 20% reduction in RBC use compared with 44 patients who received it later on.[50]

In one study, 81 coagulopathic trauma patients who were given eptacog alfa were compared with a control group from a trauma registry.[51] The cause of coagulopathy included acute traumatic haemorrhage (46 patients), traumatic brain injury (20), warfarin use (9), congenital FVII deficiency (2) and other acquired haematological defects (4). Dosage of eptacog alfa was 40–150 μg/kg. Coagulopathy was reversed in 75% of cases. In a similar study of 29 patients with traumatic haemorrhage (25 with blunt trauma), eptacog alfa (40 μg/kg, repeated once if necessary) resulted in significantly less RBC, platelet and cryoprecipitate use when compared with matched controls.[52] Similar success was reported with eptacog alfa in smaller studies of uncontrolled bleeding after trauma.[53-55]

6. Intracerebral Haemorrhage

This section covers ICH in adults. ICH in the paediatric population may be due to a variety of pathologies, some of which are unique to this age group (e.g. intraventricular haemorrhage in neonates [IVH] or ICH in infants due to congenital brain malformations). In view of such differences in underlying pathophysiology, results of studies from adult populations with ICH cannot be directly extrapolated to paediatric patients and evidence from studies conducted in the relevant paediatric population should be sought (e.g. see section 9.2.3 for neonatal IVH).

6.1 Reviews

There are two recent reviews written by the research group that conducted the RCTs in this area. They stated that the key to successful ICH treatment is to limit the haematoma growth within the first few hours of onset and thus minimize or prevent neurological deterioration, which is a predictor of increased mortality. They suggested that ultra-early therapy with eptacog alfa could be useful in this regard and cite their own phase II RCT in 399 patients (see section 6.2) where the best outcomes were achieved within 3 hours of symptom onset.[56,57] Systematic reviews have based their recommendations on the same phase II study results. In one of these, eptacog alfa was deemed appropriate for nontraumatic intracranial bleeding (only if <4 hours has elapsed since symptom onset or if traumatic bleeding is associated with anticoagulant use and haematoma expansion),[5] whilst the other commented on the significant reduction in mortality among patients with ICH.[6]

6.2 RCTs

There are three phase II RCTs, two of which investigated escalating doses of eptacog alfa and reported frequency of adverse events as the primary outcome.[58,59] In the other, larger study, 399 patients with ICH (diagnosed by CT scan within 3 hours of onset) were given eptacog alfa (40, 80 or 160 μg/kg) or placebo within 1 hour of diagnosis in an attempt to limit haematoma expansion.[7] Haematoma volume (primary endpoint) increased more in the placebo group (29% at 24 hours) than in the eptacog alfa groups (11–16%; p = 0.01). Death or disability (secondary endpoint assessed at 90 days) was also significantly reduced in the eptacog alfa groups (49–55%) compared with placebo (69%; p = 0.004) as was 90-day mortality (29% vs 18%, respectively; p = 0.02). The authors concluded that treatment with eptacog alfa within 4 hours after the onset of ICH limits the growth of the haematoma, reduces mortality and improves functional outcomes at 90 days. However, it should be noted that this study was not powered to detect clinical endpoints and the data have been contradicted by the presentation of results of the phase III RCT – FAST (Factor Seven for Acute Hemorrhagic Stroke) – at the European Stroke Conference in May 2007.[60,61] This most recent study showed a reduction in bleeding but absolutely no difference in the primary endpoint (rates of poor outcomes, defined as death or severe disability at 90 days) among 821 patients receiving eptacog alfa (20 μg/kg or 80 μg/kg) compared with placebo. The proportion of patients who died or were severely disabled at 90 days were 26%, 29% and 24% for eptacog alfa 20 μg/kg, 80 μg/kg and placebo, respectively. In addition, 90-day mortality was 18%, 21% and 19% for those in the 20 μg/kg, 80 μg/kg and placebo groups. A *post hoc* analysis of the data suggested that a subgroup of ICH patients aged <75 years may benefit from eptacog alfa treatment.

There was a small dose-related increase in the frequency of thromboembolic adverse events in the phase II study, which may have occurred due to prolonged eptacog alfa concentrations because of the relatively low bleeding rate compared with trauma.[9] The drug safety profile in the phase III study showed a small increase in cerebral and myocardial ischaemic events, but no increase in thromboembolic events.

6.3 Other Studies and Cases

There is one study of eptacog alfa in warfarinized patients with acute ICH, which is summarized in section 7.

7. Reversal of Vitamin K Antagonist (Warfarin) Therapy

Effective reversal of warfarin effect is readily achieved by the combination of cessation of warfarin, vitamin K, plasma or factor concentrate infusion, depending on the clinical circumstances. Effective rapid reversal of warfarin effect in cases of serious haemorrhage can be achieved by giving prothrombin complex concentrates and plasma infusion. The prothrombin complex concentrate available in some countries has a low content of FVII so fresh plasma must also be transfused. These therapies are indicated for this purpose and they also replace other vitamin K-dependent coagulation factor deficiencies, especially factor II, which are important contributors to bleeding in warfarinized patients. Given these considerations, eptacog alfa has no primary role in the reversal of anticoagulation in patients taking warfarin. There may be a role for the off-label use of eptacog alfa in the context of ICH or life-threatening haemorrhage not controlled by surgical or medical therapies.

7.1 Reviews

The systematic review by Levi et al.[4] summarized studies up to July 2004 on this topic (see section 7.3 for summary). They commented that the duration of effect of eptacog alfa is short (2–3 hours) and that alternative treatment with prothrombin complex concentrates will correct not only a deficiency of FVII but also deficiencies of other vitamin K proteins. In a more general review, the same research group stated that eptacog alfa may become a therapeutic option to reverse anticoagulation in cases of severe bleeding or in patients scheduled for emergency surgery, but that more investigation is required. Shander et al.[5] stated that eptacog alfa was appropriate to use in nontraumatic intracranial bleeding within 4 hours of symptom onset, with or without taking warfarin, and for isolated traumatic head injury if there was evidence of expanding bleeding in patients taking warfarin.

7.2 RCTs

There are no RCTs of the use of eptacog alfa in managing haemorrhage in warfarinized patients.

7.3 Other Studies and Cases

Levi et al.[4] summarized the uncontrolled studies and case reports about reversal of anticoagulant therapy with eptacog alfa as follows. In healthy volunteers treated with acenocoumarol, the prolonged international normalized ratio (INR) was normalized by eptacog alfa (5–320 μg/kg).[62] Doses of eptacog alfa >120 μg/kg resulted in INR normalization for >24 hours. Six patients on warfarin prophylaxis developed overt CNS bleeding and were given eptacog alfa (10–40 μg/kg).[63] It reversed anticoagulation, arrested bleeding and allowed surgical drainage of the haematoma in all patients. A study in 13 warfarinized patients undergoing invasive procedures showed that eptacog alfa (15–90 μg/kg) normalized the PT and corrected the prolonged INRs in all subjects.[64]

There are also more recent studies showing that eptacog alfa might be effective in warfarin-induced anticoagulation. In a consecutive series of seven elderly patients with symptomatic, nontraumatic warfarin-related acute ICH, the INR decreased rapidly from a mean of 2.7 to 1.08 after administration of eptacog alfa (mean dose 62.1 μg/kg).[65] Five of the seven patients survived and were discharged from hospital with severe disability. Reversal was successfully achieved in a single patient with elevated INR and PT prior to alteplase administration in acute stroke.[66] Another case involved an elderly male patient with an aortic prosthetic valve, chronic lymphocytic leukaemia and recently developed metastatic lung cancer.[67] The patient developed a major gastrointestinal bleed as a result of an elevated INR (>8) due to warfarin administration. He received eptacog alfa (50 μg/kg), which corrected the INR to 2.1 and bleeding ceased. A retrospective chart review of 28 patients with warfarin-associated

ICH treated in a neurology/neurosurgery intensive care unit has been published.[68] A total of 12 evaluable patients were given eptacog alfa (dose range 2.4–9.6 mg) after vitamin K and fresh frozen plasma (FFP) because they were classified as high risk. The results showed eptacog alfa shortened the time to correction of INR and reduced the total dose of FFP. In a retrospective controlled study, eptacog alfa was used as a second-line therapy for reversal of coagulation (mainly warfarin) in 29 neurosurgical patients after initial attempts at reversal with FFP had failed.[69] After eptacog alfa (1.4 mg), the mean INR decreased and normalized within 7 hours. The number of patients with good functional outcome (Glasgow Outcome Scale score of 5) was greater among patients treated with eptacog alfa compared with those in a matched group who received only vitamin K and FFP. There were six deaths in each group.

8. Reversal of Anticoagulant Therapy

8.1 Reviews

Shander et al.[5] stated that eptacog alfa was appropriate to use in nontraumatic intracranial bleeding within 4 hours of symptom onset, with or without warfarin or a low-molecular-weight heparin (LMWH) administration, and for isolated traumatic head injury if there was evidence of expanding bleeding in patients receiving warfarin or LMWH. While they also described the pentasaccharide studies[70,71] and other studies also described in section 8.2,[62-65,72] they did not specifically recommend a primary use in reversing anticoagulant therapy.

8.2 RCTs

An RCT (placebo-controlled crossover) was conducted in 12 healthy volunteers to investigate the use of eptacog alfa as an antidote to the long-acting anticoagulant agent idraparinux sodium.[71] One injection of eptacog alfa (90 μg/kg, 3 hours or 1 week after idraparinux sodium 7.5 mg) normalized the prolonged activated partial thromboplastin time (aPTT) and PT, and reversed the decrease in markers for thrombin generation. Therefore, eptacog alfa may reverse the peak and trough anticoagulant effects of idraparinux sodium. This result agreed with a similar study using fondaparinux sodium.[70] Thus, eptacog alfa may be an antidote to the pentasaccharide anticoagulants if serious bleeding complications arise, although studies in actual patients are required. In another RCT (single-blind, parallel-group) in 47 healthy male volunteers, eptacog alfa (90 μg/kg) or placebo was given 1 hour after the start of melagatran (12.5 mg) infusion.[73] It did not reverse the melagatran-induced effects on activated partial thromboplastin, thrombin generation and platelet activation. The authors suggest further investigation to establish whether repeated, continuous or higher doses of eptacog alfa might be effective.

8.3 Other Studies and Cases

A case report showed that combined single doses of eptacog alfa (90 μg/kg) and tranexamic acid (15 mg/kg) were effective in controlling severe postoperative bleeding after fondaparinux sodium administration.[74] The 79-year-old patient had been given fondaparinux sodium to prevent deep vein thrombosis after hip surgery but he developed haemorrhagic shock and bleeding could not be stopped by conventional measures. There is a recent report of two cases of severe sepsis treated with drotrecogin alfa where massive perioperative haemorrhage (unresponsive to conventional treatment) was treated with eptacog alfa (40 μg/kg).[75] The authors state that effective haemostasis was achieved with two doses of eptacog alfa.

9. Paediatrics

There are many clinical scenarios where eptacog alfa has been used in paediatrics; however, the studies are in small numbers of patients or in one patient only. Thus, the evidence base for using eptacog alfa in children is very limited. This section contains details from many low quality studies with low levels of evidence, and the information should be considered with that in mind, together with the data summarized in section 10. The only published RCT in the paediatric population is in cardiac surgery for congenital heart disease, which showed no benefit

of eptacog alfa prophylaxis and possibly harm (see section 9.2.2).

9.1 Reviews

Mathew and Young[76] have recently reviewed the role of eptacog alfa in both haemophilia and nonhaemophiliac bleeding conditions in children. They commented on the paucity of high levels of evidence for its off-label use in paediatrics and that extrapolation of results in haemophiliac children was not possible because of publication bias. They have attempted to consolidate results from available studies because they say it is unlikely that clinical trials in children will be conducted or completed. The studies suggested that eptacog alfa may reduce or arrest bleeding and thus may be useful in eliminating coagulopathy in surgical haemorrhage, brain injury or sepsis so that resuscitation and surgical correction of anatomical defects may be completed. However, there remain many unknown efficacy and safety issues with the drug. The summary of studies in this section was compiled from the review by Mathew and Young[76] together with recent studies identified by the literature search strategy.

9.2 Studies and Cases

9.2.1 Liver Disease

The evidence in liver failure or transplantation is from cases or case series. In one case, an 11-month-old with total parenteral nutrition-induced cholelithiasis and chronic coagulopathy developed upper gastrointestinal bleeding, which did not stop after FFP administration.[77] Administration of eptacog alfa (90 μg/kg) corrected coagulation and the bleeding subsided. Prophylactic eptacog alfa has also been successful in children with liver failure who underwent endoscopic procedures of liver biopsy.[78,79] In a study of 12 children with liver disease, eptacog alfa (median dose 66 μg/kg) decreased bleeding in 10 of 22 children with life-threatening bleeding (where conventional therapy had failed) and may have prevented bleeding complications in all seven children who underwent invasive procedures.[80] Similar success was reported in a study of children with liver failure where eptacog alfa produced rapid cessation of bleeding after conventional therapy had failed.[81]

A retrospective review of 89 children who underwent liver transplantation showed that prophylactic eptacog alfa given to a cohort of 28 children with high risk of operative bleeding reduced their risk to a similar level of a cohort of 61 children with no identified risk of bleeding.[82] In a case series, the use of eptacog alfa in seven children presenting with coagulopathy and nonsurgical bleeding after liver graft reperfusion is described.[83] A single dose of eptacog alfa (mean 68 μg/kg; aprotinin or tranexamic acid were given simultaneously) reversed severe coagulopathy developing after graft reperfusion and produced effective haemostasis in liver transplant recipients.

There is a recent report of eptacog alfa use in two children, one with end-stage renal disease (14 years old) and one with liver failure (9 months old), who had compartment syndrome related to life-threatening bleeding complications.[84] In the first case, eptacog alfa (90 μg/kg) successfully stopped bleeding, and pain, paraesthesia and sensory/motor dysfunction resolved within hours. The fasciotomy site was closed 5 days later without complication. In the second case, two bolus infusions of eptacog alfa (90 μg/kg at 4-hour intervals) produced cessation of bleeding after the second infusion and the compartment syndrome resolved within 4 hours. Scheduled fasciotomy was cancelled; however, the patient died 1 month later of fulminant liver failure.

9.2.2 Cardiac Surgery

There is an RCT on the effectiveness of prophylactic administration of eptacog alfa (40 μg/kg; a second dose was administered if bleeding was excessive and also given postsurgery if postoperative bleeding occurred) for cardiopulmonary bypass surgery in children aged under 1 year with congenital heart disease.[85] The primary endpoint was time to chest closure following reversal of heparin with protamine sulfate, and secondary endpoints were volume of transfused blood, platelet concentrates and FFP. No benefit of eptacog alfa prophylaxis was found in the time to chest closure, which was signifi-

cantly prolonged in the eptacog alfa group compared with the placebo group. Also, there were no significant differences in the secondary endpoints. The authors could not explain why prolonged chest closure occurred with eptacog alfa.

All of the other evidence in cardiac surgery is from case reports and case series. Cessation of postoperative bleeding was found in several cases and case series.[86-88] Also, there are case series showing eptacog alfa was successful (after failure of conventional treatment) at stopping bleeding following cardiac surgery with cardiopulmonary bypass (30–60 μg/kg, up to four doses),[89] after open-heart surgery (90 μg/kg)[90] and at reducing chest tube output after cardiac surgery.[91,92] Mathew and Young[76] commented that the potential for thrombotic episodes in this population group (although not evident in these cases) dictates eptacog alfa be used only when no other option is available, or should be limited to clinical trials.

9.2.3 Preterm/Term Infants

There are several case reports and series where eptacog alfa has been used in a desperate attempt to cease bleeding after standard therapies had failed.[76,93] A case report documents successful use of eptacog alfa (50 μg/kg every 3 hours) for severe pulmonary haemorrhage in a very low birthweight infant.[94]

A prospective, single-arm pilot study of ten preterm infants between 23 and 28 weeks of gestation investigated the prophylactic use of eptacog alfa in IVH.[95] This study was not powered to determine efficacy or adverse effects; however, the authors stated that administration of eptacog alfa (100 μg/kg every 4 hours for 72 hours) did not cause any adverse events and 20% of the neonates went on to have grade III or IV IVH, which was similar to the rate in studies in which eptacog alfa was not given. A recent review highlighted the potential risk of thrombosis with use of eptacog alfa for prevention of IVH in preterm infants and suggested that a prospective RCT was required before any recommendation on its use in this area could be made.[96]

A case series of nine infants, aged between 2 days and 4 months, with coagulopathy and bleeding treated with eptacog alfa has been published recently.[97] The infants all had acute life-threatening haemorrhage: two were postoperative from cardiac surgery, two had vitamin K deficiency and ICH, three had suspected necrotizing enterocolitis and abdominal haemorrhage, and two had pulmonary haemorrhage. Seven of the nine patients received FFP, cryoprecipitate or platelet administration in failed attempts to correct the coagulopathy prior to being given eptacog alfa (dose range 90–100 μg/kg). Clinical resolution of bleeding occurred in all patients after receiving eptacog alfa and seven of nine patients survived.

A recent report showed how three cases of acute life-threatening peri- and postnatal haemorrhage were successfully controlled after using eptacog alfa.[98] All infants were first treated with vitamin K, FFP and platelet transfusion. The cases substantiated other reports that eptacog alfa may be an effective treatment for acute, refractory and life-threatening bleeding in neonates and premature infants.

9.2.4 Trauma

Trauma data in children are scant. Mathew and Young[76] pointed out that patients who are haemorrhaging are also at high risk of thrombosis and must be monitored for this if they are given eptacog alfa. Also, any further doses of eptacog alfa once haemostasis is achieved in this patient group may be harmful compared with most other indications listed in this section. Of the 36 trauma patients in the Martinowitz and Michaelson[11] article (section 5.3.1), there were 13 who were 14–18 years old. They had experienced massive life-threatening bleeds that failed to stop despite conventional treatment; however, 12 responded to eptacog alfa and three died (one from blood loss and two from sepsis). In the series of 81 coagulopathic patients reported by Dutton et al.[51] (section 5.3.1), 17 were aged ≤18 years. Reversal of coagulopathy by eptacog alfa was achieved in 75% of patients and six of the 17 paediatric patients died. Three paediatric patients had severe coagulopathy after cerebral injury.[99] Administration of eptacog alfa (90 μg/kg as initial therapy or after failed conventional therapy) produced rapid and successful correction of coagu-

lopathy. In two children with traumatic liver injuries, eptacog alfa (50 μg/kg every 2 hours, following failed conventional therapy) was successful in achieving haemostasis.[100]

9.2.5 Surgery

Eptacog alfa use (100–200 μg/kg every 2 hours) has been reported in four paediatric patients (term infant, 3, 9 and 18 years) with 'surgical-type' bleeding.[101] Bleeding was stopped in two of the patients with liver and gastrointestinal bleeding, but not in the other patients (gastrointestinal bleed and graft-versus-host disease).

In a retrospective review, there were four patients (three neonates and a 3-year-old boy) who received eptacog alfa for refractory bleeding while on extracorporeal membrane oxygenation following open heart surgery.[102] Administration of eptacog alfa (90–120 μg/kg) decreased bleeding within 30 minutes and was repeated as a prophylactic measure after 4 hours. Overall, transfusion requirements fell substantially in all patients. Successful use of repeated doses of eptacog alfa was reported in a further two patients on extracorporeal membrane oxygenation (11-year-old after heart transplant and a 13-year-old with cardiopulmonary failure).[103] There is also a case of a 4-year-old girl who experienced severe postoperative bleeding from her chest tube drain after cardiac transplant surgery requiring her to receive extracorporeal membrane oxygenation.[104] After failed standard therapy, eptacog alfa (180 μg/kg) controlled the haemorrhage.

The efficacy of eptacog alfa was evaluated retrospectively in a series of 26 patients (mean age 16.6 years) with scoliosis undergoing correctional surgery. The results were compared with matched controls who received standard therapy. Intraoperative and combined intraoperative and postoperative blood losses were significantly smaller in the eptacog alfa-treated group (mean dose 23 μg/kg, 30 minutes before start of surgery) than in the historical controls. There was also reduced blood loss per vertebral segment fused and per hour of surgery. The authors suggested that eptacog alfa may be an effective haemostatic agent for spinal fusion surgery in adolescent patients with idiopathic scoliosis.[105]

9.2.6 Other Uses

Mathew and Young[76] presented many other individual cases of eptacog alfa use in children. There is an RCT of the efficacy and safety of eptacog alfa (100 μg/kg, repeated at 30 minutes if necessary) in 25 patients aged <18 years with grade II or III Dengue haemorrhagic fever who required blood component therapy for controlling bleeding episodes (primary outcome).[106] Patients received conventional therapy as well as eptacog alfa. Two hours after administration there was complete cessation of bleeding in 75% of eptacog alfa patients versus 44% on placebo. Cumulative use of RBCs was not different between the groups but the need for platelet concentrate was lower among eptacog alfa patients. This study confirmed an earlier study by the same authors that eptacog alfa might be a useful additional treatment to blood component transfusion for controlling active bleeding in children with Dengue fever, especially when platelet concentrate was not readily available.[107]

10. Safety of Eptacog Alfa

Thromboembolic adverse events are of greatest concern with eptacog alfa use, especially in patients with a history of thrombosis or with risk factors for thromboembolic disease. The simultaneous use of activated prothrombin complex concentrates or the presence of sepsis may also contribute to the occurrence of thrombosis; however, Levi et al.[4] reported use of eptacog alfa in several patients where disseminated intravascular coagulation was present without untoward outcome. Nevertheless, patients with an underlying pathology that predisposes towards thrombosis should be carefully monitored before, during and after eptacog alfa therapy.[108]

Most of the prospective studies have not shown an increase in thromboembolic events with eptacog alfa compared with placebo. However, these RCTs have been underpowered to detect a difference in this low frequency outcome in most cases.[8,17,23-26,39,40] The research group that published the RCT of eptacog alfa use in trauma patients[8] has published a *post hoc* subanalysis of 30 patients with blunt traumatic brain injury and

they report that the risk of mortality and thromboembolic adverse events was similar in those who received eptacog alfa or placebo.[109] In the phase II study of eptacog alfa in ICH by Mayer et al.,[7] a significant increase in thromboembolic events was reported most notably at the highest eptacog alfa dose (10% at 160 μg/kg, 2% for placebo). Vincent et al.[9] proposed that eptacog alfa clearance is relatively low in ICH because of the low bleeding rate compared with the severe bleeding seen in conditions such as trauma. A recent pooled analysis of the ICH trials showed there was no overall increase in the risk of total thromboembolic events except for arterial thromboembolic events at high eptacog alfa doses (120–160 μg/kg; 5.4% vs 1.7% compared with placebo; p = 0.13).[110]

In the CADTH systematic review, mortality rates associated with eptacog alfa and placebo groups in the various RCTs were given.[6] In some of the studies, mortality rates were higher in the eptacog alfa groups, although statistical significance was not found in any of the studies. The Cochrane group found a trend for reduced mortality with therapeutic use of eptacog alfa in a pooled analysis of seven RCTs (relative risk [RR] 0.82; 95% CI 0.64, 1.04).[3] However, similar analyses by the same authors showed a trend against eptacog alfa with respect to thromboembolic adverse events: RR 1.25 (95% CI 0.76, 2.07) for prophylactic use and RR 1.50 (95% CI 0.86, 2.62) for therapeutic use.

In an observational study of 655 cardiac surgery patients with excessive bleeding, adverse event rates were compared in 114 patients who met the criteria for eptacog alfa therapy (mean dose 56 μg/kg) versus 541 who did not require eptacog alfa.[111] After adjustment for confounders, eptacog alfa was not found to be associated with an increased risk of adverse events, and early eptacog alfa treatment (i.e. ≤8 units RBC before treatment) was associated with better outcomes than later treatment. In a previous and smaller study by the same investigators, an increased frequency of acute renal failure was observed in cardiac surgery patients who received eptacog alfa, but the authors admitted no definitive conclusions could be drawn because of the small sample size.[112] An RCT on prophylactic use of eptacog alfa in cardiopulmonary bypass surgery in children with congenital heart disease found no benefits and that it was associated with prolonged time to chest closure.[85]

In the systematic review by Levi et al.,[4] they estimated the incidence of thromboembolic events from all cases at 1.4% in nonhaemophiliac patients, and state that it is probably lower than this when all of the RCT data are added. A review of critical safety data obtained from 13 NovoNordisk-sponsored clinical trials of eptacog alfa in patients with coagulopathy secondary to anticoagulant therapy, cirrhosis or severe traumatic injury showed that thrombotic adverse events were reported for 5.3% (23 of 430) of placebo-treated patients and 6.0% (45 of 748) of patients on active treatment. No significant difference was found between placebo-treated and eptacog alfa-treated patients with respect to the incidence of thrombotic events, either on an individual trial basis or for all the trials combined (p = 0.57).[113]

The Haemostasis Registry has published results from their case series, which shows that thromboembolic adverse events were possibly (27 cases) or probably (2 cases) linked to eptacog alfa therapy among 694 cases; i.e. a total of 4% of cases.[13] This agrees with 9 of 285 thromboembolic complications being found in a review of eptacog alfa use in trauma patients in one institution where the authors stated that patients with arterial injuries were the most susceptible.[114]

Post-haemorrhagic hydrocephalus was recently reported in five of nine ICH cases treated with eptacog alfa.[115]

10.1 US FDA Adverse Event Reporting System

O'Connell et al.[116] looked at the US FDA Adverse Event Reporting System for approved and off-label use of eptacog alfa between March 1999 and December 2004 (across all age groups). There were 168 of 431 reports that described 185 thromboembolic events (eptacog alfa had been given as treatment in 115 of 168 reports and for prophylaxis in 46 of 168 reports). Off-label use accounted for 151

of 168 (90%) of the reports. Reported adverse events were thromboembolic cerebrovascular accident (n = 39), acute myocardial infarction (n = 34), other arterial thromboses (n = 26), pulmonary embolism (n = 32), other venous thromboses (including deep vein thrombosis; n = 42) and clotted devices (n = 10). In 36 of 50 (72%) reported deaths, the probable cause of death was the thromboembolic event. Further analysis showed that 73 events (52%) occurred in the first 24 hours after the last dose (30 events within 2 hours). Most of the reports lacked sufficient information to fully evaluate potential dosage associations, and the authors stated that RCTs are needed to establish the safety of eptacog alfa in nonhaemophiliac patients.

11. Optimum Dosages and Timing of Administration

Dosages of eptacog alfa have been stated in each of the previous sections but no definite guidelines may be given because of the lack of well designed studies. In the evidence-based review by Shander et al.,[5] the consensus panel recommended a dosage range of 41–90 μg/kg for all off-label uses.

Further studies that have specifically looked at dosage are as follows. A retrospective, multicentre chart audit of 315 nonhaemophiliac patients showed that eptacog alfa was given for prevention of bleeding (primarily related to an impending surgical or invasive procedure, 38% of patients) or for treatment of bleeding (62%). There were 89% and 74% of patients with existing coagulopathy in the prevention and treatment groups, respectively. The median doses for prevention and treatment were 76 and 89 μg/kg, respectively. Bleeding was rare with prophylactic eptacog alfa (14% bled within 6 hours of their procedure). In the treatment group, 53% stopped bleeding within 6 hours, but 26% experienced rebleeding and 37 patients died from bleeding within 48 hours after eptacog alfa administration, which is less than reported in case series in the literature and may have been related to pH or to publication bias.[117] Khan et al.[118] performed a retrospective cohort study of 13 patients with life-threatening haemorrhage (in trauma and post-operative patients) who had no known history of coagulopathic disorders. Administration of eptacog alfa occurred after conventional methods had failed. The authors used a standard dose of 90 μg/kg in six patients but noted that a reduced dose in a further five patients was also effective at stopping bleeding (overall average dose was 76 μg/kg).

12. Patient Selection

A beneficial effect of eptacog alfa in all nonhaemophiliac conditions may not be expected, not only because of the wide variation in bleeding conditions but also because of patient characteristics. Administration of eptacog alfa may produce haemostasis in some patients but they may still die of shock or rebleeding. A recommendation or guidance on which patients will be likely to benefit from eptacog alfa treatment is not currently possible.

In a retrospective study, eptacog alfa (50 or 100 μg/kg) use was reviewed among 46 patients with acute haemorrhagic shock as a result of blunt or penetrating trauma.[119] Cessation of bleeding was the outcome of interest. There were 20 patients with a transient response who died and 26 patients who did respond to eptacog alfa therapy (eight of whom died later). Independent predictors of successful response were the PT at time of administration and the revised trauma score at the time of hospital admission. Younger age and injuries in only one body area were also associated with better outcomes. The authors stated that patients with profound haemorrhagic shock (low revised trauma score, elevated PT or profound metabolic acidosis) were unlikely to respond to eptacog alfa therapy. These results confirm earlier results showing that eptacog alfa activity was reduced in acidosis (but not hypothermia),[120] and the authors agreed that 'last-ditch' administration of eptacog alfa was unlikely to be beneficial.[121] Restoration of PT is more of an indication that eptacog alfa has been given rather than being a surrogate marker for efficacy.[13]

Predicting response has also been measured by analysing mortality data. In a study of 18 patients with severe haemorrhage, the six survivors had low-

er organ failure scores than the 12 who died, and they also tended to respond to one eptacog alfa dose (90 μg/kg) with a significant reduction in blood product requirements.[122] PT or aPTT did not predict survival. The authors suggested that organ failure assessment may be useful when considering eptacog alfa treatment. A clinical scoring system was devised in another study of 36 patients with uncontrolled surgical, traumatic or obstetric bleeding.[123] The score was based on the presence of coagulopathy, renal impairment, hypothermia, transfusion of RBCs and age. Death occurred in 19 patients. Survival was more likely in younger than older patients, those with fewer co-morbidities and in patients who had needed least RBCs prior to eptacog alfa administration, although the authors admitted that more work was required to better define which patients were the most suitable for therapy.

The Haemostasis Registry has published analyses from 694 cases, reporting an association between response and the following variables: pH, temperature, platelet level, fibrinogen level, RBC units before eptacog alfa dose, PT/INR, aPTT and place of administration; however, sex, dose, age and time were not significantly associated with response.[13] The following variables were associated with mortality: low pH, low platelet level, RBC units before eptacog alfa dose, PT/INR and place of administration.[13]

13. Cost Considerations

The aim of one UK study was to assess the lifetime cost effectiveness of eptacog alfa versus placebo for control of bleeding in patients with severe blunt trauma. The authors developed a cost-effectiveness model based on patient data from an RCT. The data were supplemented with secondary data from UK sources to estimate lifetime costs and benefits. A baseline estimate of the incremental cost per life-year gained with eptacog alfa, relative to placebo was £12 613 (year of costing not stated). The incremental cost per quality-adjusted life-year (QALY) gained was £18 825 (both estimates were sensitive to discount rates and health state utility values used). Thus, eptacog alfa may be a cost-effective therapy to the UK National Health Service.[124]

In one US study, the cost effectiveness of early treatment with eptacog alfa for ICH in adults was examined using a decision-analytic model.[125] Treatment of ICH with eptacog alfa (40 μg/kg and 160 μg/kg) appeared to be cost effective (≤$US50 000/QALY) [2005 costing]. At the 80 μg/kg dose, eptacog alfa was cost effective and cost saving. Investigators in New Zealand reviewed blood transfusion over a 12-month period and assessed the major costs associated with haemorrhage management. A pharmacoeconomic evaluation of eptacog alfa intervention for large volume transfusion was conducted to identify the most cost-effective strategy for using eptacog alfa. Intervention with eptacog alfa was most cost effective earlier rather than later in the RBC transfusion period – the optimal timepoint was when 14 RBC units had been transfused.[126]

An economic analysis of the RCT in abdominal prostatectomy showed that eptacog alfa (40 μg/kg) lowered overall treatment costs and reduced surgery time by eliminating the need for transfusion.[127]

14. General Practice Points

Initial surgical and/or medical management of life-threatening bleeding should be undertaken with the following suggested protocol:

- Identification and correction of any reversible defect (such as hypothermia and acidosis).
- Surgical intervention or embolism if required.
- Appropriate transfusion of blood components (i.e. packed RBCs, FFP, platelets, cryoprecipitate). Specialist haematology input should be sought in this regard.
- Reversal of the anticoagulant effects of heparin (protamine sulfate).
- Reversal of the anticoagulant effects of warfarin (prothrombin complex concentrates/FFP and vitamin K).
- Administration of pharmacological agents (e.g. fibrinolytic inhibitors).

- Regular monitoring of full blood count, PT, aPTT, fibrinogen and D-dimer.

In 'exceptional' cases[1] where patients have continued life-threatening bleeding despite appropriate conventional surgical and/or medical treatment to control bleeding, eptacog alfa may be considered as additional therapy. The amelioration of thrombocytopenia (target platelets >50 000 × 10^9/L), coagulopathy (target fibrinogen >1.0 g/L), acidosis (pH >7.2), anaemia (haematocrit >24%) and hypothermia is desirable for eptacog alfa to be effective. Use of eptacog alfa as a 'last-ditch' effort in the absence of conventional treatment is not recommended.[121]

15. Conclusion

There is good evidence from systematic reviews and RCTs to support the use of eptacog alfa in ICH in adults if it can be given within 4 hours of symptom onset. Data from a recent phase III RCT has called into question the beneficial mortality and functional outcomes observed in an earlier phase II study; however, *post hoc* analysis suggests that patients aged <75 years may benefit.

There is less robust evidence to support the use of eptacog alfa for life-threatening bleeding in liver, cardiac or other surgery patients and in patients with blunt trauma. In these circumstances, it should only be given as additional therapy to surgical and/or medical control of bleeding (only as part of a clinical trial or in 'exceptional' situations when other therapies have failed). The evidence for use of eptacog alfa in penetrating trauma is lacking.

There is good evidence against the prophylactic use of eptacog alfa in OLT or liver resection, or in variceal and nonvariceal haemorrhage in patients with cirrhosis. Conflicting RCT results exist for the prophylactic use of eptacog alfa in elective surgery; therefore, it cannot be recommended in this situation. There is insufficient evidence for a primary role of eptacog alfa in reversal of anticoagulation with heparin-like molecules and novel anticoagulant agents. There are effective therapies that correct all warfarin-induced factor deficiencies, and off-label use of eptacog alfa for warfarin reversal should only be considered in the context of ICH.

The evidence for use of eptacog alfa in children is poor (mostly case studies or series). The only published RCT is in cardiac surgery for congenital heart disease where no benefit but possible harm was documented with eptacog alfa prophylaxis. Nonetheless, it may be of benefit in some children with life-threatening bleeding in the context of trauma, surgery or liver disease (used as additional therapy when maximal surgical and/or medical control of bleeding has failed) but the overall benefit-risk ratio may be unfavourable if there is an underlying risk of thromboembolism (e.g. trauma, congenital heart disease, other hyperviscous or hypercoagulable states, or presence of arterial or central venous catheters).

Thromboembolism may be associated with eptacog alfa use. Although the magnitude of this risk and possible predisposing factors are not clearly delineated, some data suggest increased risk at higher doses. Pooled analysis of RCTs shows variable effects of eptacog alfa use on mortality. Data from some observational studies and postmarketing surveillance suggest an increased risk of thromboembolism associated with off-label uses. Further well designed studies are required to assess more definitively the risk of thromboembolism with eptacog alfa and better determine its effects on mortality.

For each nonhaemophiliac condition, neither the optimum dosages nor the optimum timing of administration is defined. Similarly, which patients will be most likely to benefit in terms of haemostatic efficacy and mortality is not clear. Certain procedures are recommended before giving eptacog alfa, including conventional measures to stop bleeding, such as surgery and blood transfusion, correction of hypothermia and acidosis, and reversal of anticoagulation. The outcomes (effectiveness and safety) of all off-label uses should be systematically evaluated and reported. Further data to better assess the cost effectiveness of eptacog alfa in off-label indications are required.

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