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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
RESULTS	6
DISCUSSION	7
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	9
CHARACTERISTICS OF STUDIES	14
APPENDICES	14
WHAT'S NEW	15
HISTORY	15
CONTRIBUTIONS OF AUTHORS	16
DECLARATIONS OF INTEREST	16
SOURCES OF SUPPORT	16
INDEX TERMS	16

[Intervention Review]

Recombinant human activated protein C for severe sepsis in neonates

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ABSTRACT

Background

Sepsis is a common problem in preterm and term infants. The incidence of neonatal sepsis has declined, but mortality remains high. Recombinant human activated protein C (rhAPC) possess a broad spectrum of activity modulating coagulation and inflammation. In septic adults it may reduce mortality, but no significant benefit has been reported in children with severe sepsis.

Objectives

To determine whether treatment with rhAPC reduces mortality and/or morbidity in neonatal sepsis.

Search methods

For this update searches were carried out in May 2011 of the Cochrane Central Register of Controlled Trials (*The Cochrane Library*), MEDLINE, EMBASE, CINAHL, and abstracts of annual meetings of the Pediatric Academic Societies. Doctoral dissertations, theses and the Science Citation Index for articles on activated protein C were searched. No language restriction was applied.

Selection criteria

Randomized or quasi-randomized trials, assessing the efficacy of rhAPC compared to placebo or no intervention as an adjunct to antibiotic therapy of suspected or confirmed severe sepsis in term and preterm infants less than 28 days old. Eligible trials should report at least one of the following outcomes: mortality during initial hospital stay, neurodevelopmental assessment at two years of age or later, length of hospital stay, duration of ventilation, chronic lung disease, periventricular leukomalacia, intraventricular haemorrhage, necrotizing enterocolitis, bleeding, and any other adverse events.

Data collection and analysis

Review authors were to independently evaluate the articles for inclusion criteria and quality, and abstract information for the outcomes of interest. Differences were to be resolved by consensus. The statistical methods were to include relative risk, risk difference, number needed to treat to benefit or number needed to treat to harm for dichotomous and weighed mean difference for continuous outcomes reported with 95% confidence intervals. A fixed effect model was to be used for meta-analysis. Heterogeneity tests, including the I^2 statistic, were to be performed to assess the appropriateness of pooling the data.

Main results

No eligible trials were identified. In October 2011 rhAPC (Xigris®) was withdrawn from the market by Eli Lilly due to a higher mortality in a trial among adults. Xigris® (DrotAA) (rhAPC) should no longer be used in any age category and the product should be returned to the distributor.

Authors' conclusions

Despite the scientific rationale for its use, there is insufficient data to use rhAPC for the management of severe sepsis in newborn infants. Due to the results among adults with lack of efficacy, an increase in bleeding and resulting withdrawal of rhAPC from the market, neonates should not be treated with rhAPC and further trials should not be conducted.

PLAIN LANGUAGE SUMMARY

Recombinant human activated protein for severe sepsis in neonates

Sepsis (a generalized blood stream infection) is common in neonates. Severe sepsis carries a high mortality and morbidity even with current critical care management. Activated Protein C (APC) is a protein formed within the human body to prevent formation of blood clots and helps in breaking down clots. Recombinant human APC (rhAPC) is a synthesized version of APC using recombinant technology. It has been shown to reduce mortality in severe sepsis in adults. The review authors investigated whether treatment of severe sepsis in newborn infants with rhAPC will help to reduce mortality and severe morbidity. The review authors found no controlled studies in this age group. On October 25, 2011 rhAPC (Xigris®) was withdrawn from the market by Eli Lilly due to side effect in adults. RhAPC should no longer be used in any age category and the product should be returned to the distributor.

BACKGROUND

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) in the presence of, or as a result of, suspected or proven infection (Bone 1992; Levy 2003; Weigand 2004; Goldstein 2005). Severe sepsis is defined as sepsis with one of the following features: cardiovascular organ dysfunction, acute respiratory distress syndrome (ARDS), or dysfunction of two or more organs (Goldstein 2005). The neonate is more susceptible to infections due to an immature immune system (Lewis 2001; Kapur 2002). Bacterial sepsis is the leading cause of neonatal mortality, affecting 32,000 live births annually in the USA (Stoll 1998). The definition of early and late onset sepsis varies with early sepsis defined as < 72 hours, < 4 days and < 7 days depending on the author (Klein 2001; Edwards 2002; Stoll 2004; Lukacs 2004). The increasing survival of very low birth weight (VLBW) infants has resulted in a cohort of infants at increased risk for recurrent infections. Even after reductions in mortality due to advances in supportive care and introduction of maternal intrapartum antibiotic prophylaxis, the mortality rate for both early and late onset neonatal sepsis is still high (Stoll 2002; Stoll 2003; Lukacs 2004). Infections among VLBW infants are associated with high mortality, poor growth and poor neurodevelopmental outcomes (Stoll 2004).

The pathophysiology of sepsis involves activation of immunologic defence systems including complement, pro-inflammatory, anti-inflammatory, procoagulation, anticoagulation, fibrinolytic and immunological cascades in the presence of endotoxins or microbiological products. Although the host pro-inflammatory response is an essential response in the defence against invading organisms, if it is inadequate or excessive or if anti-inflammatory response is predominant, it can lead to apoptosis, organ failure and death. Formation of microvascular thrombi and resultant anticoagulation mechanisms have a role in organ dysfunction and disseminated intravascular coagulation. When thrombin is coupled with an endothelial cell glycoprotein called thrombomodulin, it converts protein C to its activated form. Activated Protein C (APC) promotes fibrinolysis by inhibiting plasminogen activator inhibitor-1 (PAI-1) and thrombin activatable fibrinolysis inhibitor. APC inhibits thrombosis by inhibiting factors Va and VIII a. It has anti-inflammatory actions through the inhibition of pro-inflammatory cytokine release by blocking tumor necrosis factor (TNF) production and adhesion to selectins. However, APC has a short half-life, and the pool of circulating protein C is rapidly depleted in severe sepsis, as conversion to the activated form is impaired. This shifts the homeostatic balance towards greater systemic inflammation, intravascular coagulation and multiorgan failure. There is increased mortality with greater reduction of APC. Administration of APC, but not protein C, can theoretically limit microvascular injury and thrombosis (Yan 2001; Healy 2002; Hotchkiss 2003; Aird 2004; Balk 2004; Jagneaux 2004; Rice 2005). However in newborn infants the levels of Protein C are much lower than in adults and there is some suggestion that replacement may be beneficial. (De Carolis 2008; De Carolis 2010; Decembrino 2010).

The outcome of sepsis is influenced by the timeliness of administration of appropriate therapy. Greater understanding of the pathophysiology has identified multiple potential therapeutic targets for interventions to improve outcome in patients with sepsis. Modifiers of the pro-inflammatory and anti-inflammatory strategies like anti-TNF monoclonal antibody, anti endotoxin antibodies and interleukin-1 receptor antagonist have not been

effective (O'Brien 2003; Marshall 2004; Balk 2004). The coagulation and fibrinolytic abnormalities seen in sepsis have also been targeted. However, trials of anti-thrombin III, recombinant tissue plasminogen activator (rTPA), tissue factor pathway inhibitor (TFPI) and PAI-1 have been disappointing (Healy 2002; Hotchkiss 2003; Rice 2004; Zuppa 2004; Balk 2004; Gluck 2004; Rice 2005). Pentoxifylline, an anti TNF agent, has been shown to be beneficial in preterm infants (Lauterbach 1999). Intravenous immunoglobulin for prevention of neonatal sepsis does not decrease mortality, whereas its use for treatment of suspected or proven infection may decrease mortality (Ohlsson 2004a; Ohlsson 2004b).

A form of recombinant human Activated Protein C (rhAPC) called Xigris® or Drotrecogin Alfa (activated) (DrotAA) was studied in adults with severe sepsis [Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial] (Bernard 2001). There was a 6.1% absolute risk reduction in 28-day all-cause mortality, but an increase in serious bleeding complications (3.5% absolute incidence) were noted in the treatment group compared with the placebo group (2.0%). The number needed to treat to prevent one death, extrapolated from the PROWESS trial, was 16. The major adverse effect found in this and in the "Extended Evaluation of recombinant human Activated Protein C United States Trial" (ENHANCE US), a single arm, phase 3B, multicenter study of Drotrecogin alfa (activated) (DrotAA) in severe sepsis, was bleeding. The number needed to harm (for serious bleeding) was 66 (Bernard 2004).

Although a variety of scales have been used to assess severity and predict risk (some incorporating organ dysfunction, such as Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential (sepsis-related) Organ Failure Assessment (SOFA) in adults, Pediatric Index of Mortality (PIM) and Pediatric Risk of Mortality III (PRISM III) in children and Clinical Risk Index for Babies (CRIB) and Score for Neonatal Acute Physiology II (SNAP II) in neonates), there are no easy to use, standardised scales (Knaus 1985; Network 1993; Vincent 1996; Pollack 1996; Shann 1997; Richardson 2001; Goldstein 2005). RhAPC has been approved for use in the USA and EU and is currently indicated for the reduction of mortality in adults with severe sepsis who are at high risk for death with multiple dysfunctional organs or high APACHE II scores (Knaus 1985; Manns 2002; FDA 2002; EMEA 2002; Bernard 2004). The Surviving Sepsis Committee has recommended use of rhAPC for the management of severe sepsis in adults. (Carcillo 2002; Carcillo 2003; Dellinger 2004; Parker 2004; Parker 2005; Dellinger 2008). Neonates have a higher mortality for sepsis than older children or adults, and hence is likely to show more benefit to an advantageous therapy. There are several case reports and trials of rhAPC use in severe sepsis in children and neonates with apparent clinical benefit (Rawicz 2002; Barton 2004; Sajan 2004; Stroehler 2004; Parker 2005). However, newborn infants with sepsis are at increased risk for major bleeding, and hence appropriate checks are warranted to prevent indiscriminate use.

Prevention of sepsis remains the key in reducing the mortality and as stressed in the Cochrane review of "Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants" neonatal critical care units with high nosocomial infection rates may want to compare and adjust their infection control policies to those settings with low rates using benchmarking techniques (Horbar 2001; Ohlsson 2004a). Attention to simple measures like hand hygiene and central line care should be the first line of defence and may prevent some infections. The

use of adjunctive treatments like rhAPC may be considered in early onset sepsis and the cases of nosocomial sepsis occurring in spite of preventive measures.

Despite advances in critical care and introduction of newer treatments, the mortality related to sepsis among neonates remains high. In our search for newer adjunctive treatments to further reduce mortality of severe sepsis in neonates, rhAPC may be a potential addition to the armamentarium.

OBJECTIVES

Primary Objective:

To determine the effect of intravenous rhAPC as an adjunct to antimicrobial therapy and conventional critical care management on mortality (to 28 days of age) in neonates with suspected or confirmed severe sepsis.

Secondary objectives:

To determine the effects of rhAPC for treatment of neonates with suspected or confirmed severe sepsis on:

1. adverse neurological outcome at 18 months of age or later;
2. the length of hospital stay to discharge in survivors;
3. the duration of ventilation, development of chronic lung disease, intraventricular haemorrhage, periventricular leukomalacia and necrotizing enterocolitis;
4. safety of rhAPC; adverse effects attributable to its use (e.g. bleeding).

Subgroup analysis:

1. differences in outcome based on gestational age, birth weight, time of onset of sepsis, on severity of sepsis and also based on the type of infecting microorganism.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized controlled trials.

Types of participants

Newborn infants and neonates (< 28 days old, at any gestational age or birth weight) with confirmed or suspected severe sepsis and treated with antimicrobials.

- Confirmed sepsis is defined as clinical signs and symptoms consistent with infection and microbiologically proven, with a positive blood culture, CSF culture, urine culture (obtained by a suprapubic tap) or culture from a normally sterile site (e.g. pleural fluid, peritoneal fluid or autopsy specimens) for bacteria, virus or fungi
- Suspected sepsis is defined as clinical signs and symptoms consistent with sepsis without isolation of a causative organism
- Severe sepsis as evidenced by organ dysfunction (need for mechanical ventilation, hypotension or perfusion abnormalities, or need for inotrope or vasopressors or two or more organ dysfunction - liver, renal, coagulation, neurological or hematological abnormalities)

Types of interventions

Intravenous rhAPC in any dosage and any duration used as an adjunct to treat suspected or confirmed severe neonatal sepsis (treatment group) compared with placebo, or no intervention or any control non-experimental treatment other than rhAPC in the control group. Studies will be eligible whether or not other known treatments for sepsis (e.g. antibiotics, antifungal or antiviral medications) or respiratory support (with positive pressure ventilation or high frequency ventilation) or hemodynamic support were provided during the period of rhAPC treatment.

Types of outcome measures

Primary outcomes

The primary outcome is effect on 28 day all-cause mortality.

Secondary outcomes

1. All-cause mortality during hospital stay.
2. Severe disability, defined as any of blindness, deafness, cerebral palsy or cognitive delay (score more than two standard deviations below the mean for a recognized psychometric test for neurodevelopmental outcome assessed by a validated test, e.g. Bayley Scales), or adverse neurological outcome, at 18 months of age or later. These outcomes will be reported both as a composite outcome and individually (see 11 -15).
3. Length of hospital stay in survivors to discharge.
4. Duration of assisted ventilation through an endotracheal tube in days (in all patients and in survivors).
5. Chronic lung disease (CLD) defined as requiring supplemental oxygen at 28 days of age and at 36 weeks postmenstrual age.
6. Intraventricular haemorrhage; any grade and grade III and IV (Papile 1978).
7. Periventricular leukomalacia (cystic changes in the periventricular areas).
8. Necrotizing enterocolitis (NEC): all Bell stages; stage 3 - 4 or need for surgery (Bell 1978).
9. Retinopathy of prematurity (ROP): all stages; stage 3 - 5 or need for surgery.
10. Nosocomial infections.
11. Blindness.
12. Deafness.
13. Cerebral palsy.
14. Cognitive deficit.
15. Adverse effects attributable to rhAPC [e.g. hemorrhage (intraventricular hemorrhage, bleeding from venepuncture or arterial puncture sites, hematuria, gastro-intestinal bleeding, pulmonary hemorrhage)].
16. Post hoc analyses will be considered for adverse effects reported by the authors but not identified a priori in this protocol.

Search methods for identification of studies

We used the search strategy of the Cochrane Neonatal Review Group (CNRG). Relevant trials (RCTs and quasi-RCTs) were searched in the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 3, 2005), MEDLINE (January 1966 to July 2005), PRE MEDLINE (current), EMBASE (January 1980 to July 2005), LILACS (1982 to July 2005) and CINAHL (January 1982 to July 2005), the Oxford Database of Perinatal Trials and the CNRG's Neonatal

Trials Register. Computerized searches were carried out by both the authors independently. MeSH search terms (all headings): activated protein C OR Xigris OR Drotrecogin Alpha OR DrotAA OR rhAPC AND (sepsis OR septicemia OR septicemia OR septic shock OR infection OR sepsis syndrome); limits: age groups, newborns; publication type, clinical trials. Also searches were made through Gateway (<http://gateway.nlm.nih.gov/gw/Cmd>). We also searched in a variety of ways to make sure that we did not miss any studies.

For this update the searches were repeated in May, 2011.

```
# 1 explode 'sepsis' [all subheadings in MIME, MJME]
# 2 sepsis or septicemia or septicemia or sep* or septic or infection
# 3 # 1 or # 2
# 4 severe
# 5 # 3 and # 4
# 6 explode 'infant - newborn' [all subheadings in MIME, MJME]
# 7 Newborn* or Neonat*
# 8 # 6 or # 7
# 9 # 5 and # 8
# 10 "activated protein C" [all subheadings on MIME, MJME]
# 11 protein C
# 12 Xigris
# 13 "Drotrecogin alpha activated"
# 14 Drotrecogin*
# 15 # 10 or # 11 or # 12 or # 13 or # 14
# 16 # 9 and # 15
No language restriction was applied.
```

Additionally we searched abstracts of proceedings of Pediatric Academic Societies (American Pediatric Society, Society for Pediatric Research) and European Society for Paediatric Research (1990 to 2011), the database of dissertation abstracts, relevant doctoral theses and dissertations, conference and symposia proceedings, the bibliography of selected articles and journal hand searching in the English Language. Forward searches were made using SciSearch with key articles. Contacts were made with manufacturers of rhAPC, Eli Lilly Pharmaceuticals Inc. (www.lilly.com, www.lillytrials.com, www.xigris.com), authors of previously published works and subject experts for any unpublished material or to provide additional data and for ongoing trials. Also the Pharmaceutical and clinical pharmacology databases, e-PIC core, Ceutad and new products of Royal Pharmaceutical Society, International Pharmaceutical abstracts (IPA) of the American Society of Health System Pharmacists. We searched the web sites of the following organizations and other web sites: American Academy of Pediatrics (www.aap.org); Australian clinical trials registry (www.actr.org.au); Medical Research council trials register (www.mrc.ac.uk); UK national research registry (www.update-software.com/national); Food and Drug administration (www.fda.gov); Health Technology Assessment (www.nchta.org); International Sepsis Forum (www.sepsisforum.org); Society of Critical Care Medicine (www.sccm.org); American Thoracic Society (www.thoracic.org); Infectious Diseases Society of America (www.idsociety.org); European Society of Clinical Microbiology and Infectious Diseases (www.escmid.org); European Society of Intensive Care Medicine (www.esicm.org); European Society of Emergency Medicine (www.diesis.com/eusem); www.centerwatch.com; www.trialscentral.org; www.controlled-trials.com and www.clinicaltrials.gov. We attempted to identify

all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

In May, 2011, we updated the search. See: [Appendix 1](#)

Data collection and analysis

STUDY SELECTION

We used the standardized review methods for conducting a systematic review, as described in the Cochrane Collaboration Handbook and CNRG Guidelines for Reviewers and Editors for assessing the methodological quality of the studies. We independently assessed the titles and the abstracts of studies identified by the search strategy for eligibility for inclusion in this review using pre-determined criteria based on the inclusion criteria. We obtained the full text version for assessment if this could not be done reliably by title and abstract. We compared the results and resolved any disagreements by discussion and consensus. We requested additional information from corresponding study authors. We obtained full text versions of all included studies were for quality assessment.

ASSESSMENT OF METHODOLOGICAL QUALITY

If studies were located that met our inclusion criteria, we planned to independently rate each of the elements of methodological quality using the standard criteria developed by the CNRG and information were to be collected regarding details of the method of randomisation (generation of allocation sequence), stratification of allocation, allocation concealment (masking of randomisation), masking of the drug intervention, masking of the outcome assessment, completeness of follow-up, whether intention to treat analyses were possible from the available data and if the number of patients lost to follow up or subsequently excluded from the study were recorded, causes for drop outs and exclusions from the trial and whether the trial was single or multi-centered. Allocation concealment was to be graded A, B or C (A - Adequate allocation concealment, B - Uncertainty about whether the allocation was adequately concealed and C - Inadequate allocation concealment). Forms were designed for trial inclusion /exclusion, data extraction and for requesting additional information from authors of the original reports.

DATA EXTRACTION

Ranjit Kylat (RK) drew up a standard data extraction form and Arne Ohlsson (AO) validated it. If studies were located that met our inclusion criteria, we were to independently extract data using the data acquisition forms and were to contact the authors of trials to provide missing data where possible and necessary. RK was to enter the data into the computer and AO was to check the data and compare for any differences, which were then to be resolved by discussion. We were to use data extraction of sample characteristics to cross check the validity of the randomisation process.

DATA ANALYSIS

If studies were located that met our inclusion criteria, statistical analyses were to be performed according to the recommendations of the CNRG. Analyses were to be done for all infants, and for the sub-groups defined under 'Criteria for considering studies for this review'. All infants randomised were to be analyzed on 'an intention to treat basis' irrespective of whether or not they survived to receive their allocated treatment completely. Study

investigators were to be contacted to obtain unpublished data for all patients randomised but not analyzed on an intention to treat basis. Treatment effects in the individual trials were to be analyzed. Heterogeneity of treatment effects between trials were to be assessed to check the appropriateness of pooling data and performing meta-analyses. The statistical package (RevMan 5.1) provided by the Cochrane Collaboration was to be used. For dichotomous categorical outcomes, a pooled estimate of treatment effect for each outcome across studies was to be calculated as typical relative risk (RR) and typical risk difference (RD). For continuous outcomes, weighted mean difference (WMD) for change from baseline or post-treatment values was also to be calculated. Ninety five per-cent confidence intervals were to be used for each measure of treatment effect. If there was a statistically significant reduction in RD then the number needed to treat (NTT) was to be calculated. Results of the I^2 statistic were to be reported. We planned to perform a sensitivity analysis based on the methodological quality of the studies, including and excluding quasi-randomized studies.

Additional subgroup analyses were planned a priori for separate estimation of effect size including only the trials which were double masked. The following sub-group analyses were planned for the intravenous Activated Protein C versus no treatment or Activated protein C versus placebo:

1. gestational age: i) preterm neonates (< 37 completed weeks gestation) ii) term infants ($\geq$ 37 completed weeks of gestation);
2. gestational age: i) < 30 weeks ii) $\geq$ 30 weeks;
3. birth weight: i) < less than 1500 g ii) 1500 to 2500 g iii) $\geq$ 2500 g;
4. time of onset of sepsis: i) early onset sepsis (sepsis < 72 hrs) ii) late onset sepsis (sepsis $\geq$ 72 hrs); another definition of early versus late infection will also be included with cutoff < 7 days and $\geq$ 7 days;
5. suspected or confirmed sepsis;
6. severity of sepsis i) dysfunction of two organs ii) dysfunction of more than four organ systems; or i) medications needed for hemodynamic support ii) no medication for hemodynamic support needed;
7. type of organism identified: i) bacterial ii) fungal iii) viral.

A sensitivity analysis was planned, including only trials which were truly randomised. We planned to explore the funnel plots to look for evidence of publication bias.

RESULTS

Description of studies

No randomised controlled trials (RCT) or quasi RCTs studies were found meeting the inclusion criteria for this review.

However, we did identify a number of studies using rhAPC in children, that are discussed below and may be important as a background to the development and design of possible future trials in neonates. We chose to report on these as 'excluded studies' under this heading of 'Description of studies' even if they apply to populations that are older than 28 days or include study designs other than RCTs. These studies were identified through the same search strategy of the literature as for neonates, but without an age restriction.

Case reports, retrospective case series and non-randomised trials of use of rhAPC in the pediatric population

Rawicz described the use of rhAPC in a full term neonate weighing 2750 g with early onset enterococcal sepsis, multiorgan dysfunction and disseminated intravascular coagulopathy. Six hours after the start of therapy, coagulation parameters returned to normal. Apart from pyloric stenosis surgery at five weeks, the infant had a normal recovery (Rawicz 2002). There are case reports of a four day old 35 week gestational age neonate with severe Group B streptococcal sepsis and multiorgan dysfunction, who was treated with rhAPC and had an uneventful recovery (Strohler 2004) and its use in a teenage girl with sepsis (Manco-Johnson 2004). Sajan et al describes use of rhAPC in a four month old infant weighing 3500 g with Gram negative septic shock with *Serratia Marcescens*. This patient had no apparent adverse effects during rhAPC infusion and recovered, but had transient systemic hypertension and incidental detection of bilateral small occipital hemorrhages 22 days after infusion (Sajan 2004). Wyss reports retrospective data of six open label reports of rhAPC use in children (newborn to 18 years). Details of the number of subjects less than 28 days and their outcomes are awaited (Wyss 2004). There was a case series of the use of rhAPC in three children outside the neonatal age group with meningococcal purpura fulminans, two of whom survived without any adverse effects (Martinon-Torres 2004). A 12 day old neonate with group B Streptococcal septic shock was treated with 24 micrograms/kg of rhAPC for 96 hours and the infant recovered without any adverse effects (Frommhold 2005). There is a report of a seven year old girl with peritonitis, septic shock and multiorgan failure, treated successfully with DrotAA (Verre 2005).

There is a report of the use of DrotAA in a three day old neonate with septic shock and multiorgan system failure dramatic improvement in hemodynamic parameters within a few hours of administration (Albuali 2005). A further report on two patients, five months and 15 months old showed no adverse effects (Lokeshwar 2006).

Prospective non-randomised studies of use of rhAPC in the pediatric population

The Global ENHANCE trial was conducted in 400 sites in 25 countries. These 71 sites enrolled 195 pediatric patients in a single arm study (with no controls) (Vincent 2003; Eli Lilly 2005a; Vincent 2005; Goldstein 2006). All cause mortality was 26.4 %. Separate pediatric data were not published, but of the 195 enrolled children, 188 received rhAPC and data from 187 were analyzed (one was lost to follow up and not included in efficacy analysis). There were 43 (23%) children less than one year (the number less than 28 days is unknown); 28 day mortality was 14% in this group. 58/188 (30.9%) experienced serious bleeding during the 28 day study period. 6/188 (3.2%) experienced a serious adverse event that was considered to be study drug related, and one resulted in death. All serious adverse events were due to bleeding (Eli Lilly 2005a; Goldstein 2006).

An open label multicenter non-randomized, sequential pediatric trial (EVAO) of rhAPC included 83 children (term newborns to 18 years of age) (Barton 2004). In this two part study, pediatric patients with severe sepsis (by PIM score) received sequential escalating dose of rhAPC. Outcome measures were plasma pharmacokinetics, concentration and clearance, D-dimer, protein C, antithrombin levels and safety information. The second part of the study used age specific infusion rates based on data from the first part of the study. No clinical endpoints, including mortality, were considered.

All patients had coagulopathy with raised D-dimers and eighty one percent had acquired protein C deficiency. The number of patients less than one month is not known, and none of the outcomes of interest were evaluated. Overall serious bleeding events (4.8%) and mortality at 14 days (9.6%) were not statistically different from the 10.8% mortality predicted by the PIM score.

Randomized trials of rhAPC use in the pediatric population

The RESOLVE trial (Resolution of organ failure in pediatric patients with severe sepsis) in children with severe sepsis was a large multicenter trial, initiated in November 2002 with a planned enrolment of six hundred children (Dalton 2003; Eli Lilly 2005b; Nadel 2007). The study enrolled 477 patients, 237 received placebo and 240 received Drotrecogin alfa (activated) rhAPC, but two patients in the placebo and one patient in the DrotAA group did not complete the study. There was no difference in the 28 day all-cause mortality [17.2% (41/239)] in the DrotAA group and [17.5% (41/235)] in the placebo group with a relative risk of 1.06 (95% CI 0.66 to 1.46) for Drot AA compared with placebo. There was no difference in the primary endpoint, which was the composite time to complete organ failure resolution (CFTOR). Of note, the incidence of central nervous system bleeding in the DrotAA group was 4.6% (11 patients) compared to 2.1% (5 patients) in the placebo group ($p = 0.13$) (Nadel 2007).

Risk of bias in included studies

Not applicable, as no eligible studies were found meeting the inclusion criteria for this review.

Effects of interventions

No results are reported as we did not find any studies that met the inclusion criteria for this review. We did not identify any eligible trials that tested the efficacy of rhAPC in the treatment of severe sepsis in neonates. However, we did identify a number of studies using rhAPC in children which are described in detail in the "Description of studies" section above.

DISCUSSION

The mortality and morbidity from neonatal sepsis remains high. Antimicrobials are obviously the mainstay of therapy, but there is a concerning increase in the incidence of multidrug resistant organisms (Stoll 2002; Stoll 2004). Improved understanding of pathophysiological processes in sepsis gives compelling and logical reasons that, as an adjunct to antimicrobials and traditional critical care, modulating the pro-inflammatory, anti-inflammatory, coagulant, fibrinolytic and immune mechanism may help in reducing the mortality and morbidity in severe sepsis, especially in the preterm and low birth weight infant. To date, there is no single agent, apart from antibiotics, antiviral and antifungal treatment, that has convincingly shown in reproducible RCTs to be an effective adjunctive therapy in neonatal sepsis.

In a systematic review, Carr reported that there was insufficient evidence to support use of G-CSF or GM-CSF either as treatment of neonatal sepsis, or as prophylaxis to prevent systemic infection in high risk neonates (Carr 2005). Similarly, Ohlsson et al concluded that there was insufficient evidence to support the routine administration of IVIG for neonatal sepsis (Ohlsson 2004b). Pentoxifylline had shown promise as an adjunctive agent in the treatment of neonatal sepsis. Treatment with pentoxifylline led to

a statistically significant reduction in mortality in preterm neonates with confirmed late onset sepsis (Lauterbach 1999). However, caution must be exercised in interpreting the results because there were methodological weaknesses and the results have not been reproduced outside the single centre where it was studied (Haque 2005).

The search strategy used for this review identified retrospective case reports, prospective open label data and one randomised controlled trial in children, but no randomised clinical trials with any relevant clinical outcomes in neonates. Three case reports on use of rhAPC in severe neonatal sepsis reported no major adverse effects (Rawicz 2002; Frommhold 2005; Albuali 2005). There was a single prospective non-randomized study in children that was open label and designed for the evaluation of safety, pharmacokinetics and pharmacodynamics of rhAPC in children (Barton 2004). The only randomized clinical trial (RESOLVE) in children with severe sepsis was terminated earlier than the planned 600 patients had been enrolled (Eli Lilly 2005b; Nadel 2007). Of note, a trial to examine the effects of rhAPC in 11,000 low risk adult patients (Early stage severe sepsis or ADDRESS trial) was terminated due to lack of efficacy (Deans 2004). The results of this study, show no beneficial treatment effect, but there was an increased incidence of serious bleeding complications, indicating that rhAPC should not be used in adults with severe sepsis who are at low risk for death, such as those with single-organ failure or an APACHE II score less than 25 (Abraham 2005).

In adult patients with severe sepsis, economic evaluation and systematic effectiveness reviews of the use of rhAPC has shown to rhAPC to be beneficial, but significant concerns still exist (Manns 2002; Warren 2002; Fowler 2003; Girbes 2003; Eichacker 2003; Angus 2003; NICE 2004; Catalan 2004; Green 2005). The drug is currently licensed only for the FDA approved indication - severe sepsis in the adult patient with high mortality risk. There is only one case report of its use in a pregnant 19 year old woman at 18 weeks of gestation, who had septic shock with no adverse effects on mother or fetus (Medve 2005). The mortality rates of severe sepsis in children are much lower than in adults with severe sepsis (ranging from 7% to 12%) (Kutko 2003). The case fatality rate of severe sepsis in neonates (reported range: 9.6% to 13.5%) is comparable to other age groups in childhood (10.3%), but the mortality rates can be variable and depends on whether the predominant population is ELBW and preterm infants or previously healthy full term infants (Watson 2003). There are very few large epidemiologic studies addressing the severity of neonatal sepsis, but the incidence of multiorgan dysfunction is thought to be high in neonatal sepsis. Overall sepsis related mortality in newborn infants is much less than in adults, and the benefit of rhAPC when used as an adjunct may not be significant unless large numbers are enrolled. The incidence of thrombocytopenia, coagulation dysfunction and disseminated intravascular coagulation is extremely high in neonates with severe sepsis and rhAPC may be contraindicated in such situations. The use in adults with high risk of death is still recommended by many intensivists (Toussaint 2009), but there are increasing questions about its benefits (Marti-Carvajal 2011) and the results from earlier studies in adults have been questioned (Opal 2007).

There are studies done looking at different dosing regimens and for other indications (Levi 2007; Shorr 2010; Cesana 2010; Levi 2011). There are also studies done to look at other adjuvants like heparin

and corticosteroids (Levi 2007; Zimmerman 2011) the use of Protein C concentrate in neonates (De Carolis 2010; Decembrino 2010). Given that we found no randomized controlled trials which use rhAPC in severe sepsis in neonates this systematic review does not establish if the administration of rhAPC to neonates with severe sepsis is detrimental or beneficial. The randomized trial done in children had very few neonates enrolled without any separate outcome data. Thus the efficacy of rhAPC treatment for severe neonatal sepsis has not been adequately evaluated to date.

For this update in 2011 we did not identify any new trials conducted among neonates. The use of rhAPC is discouraged. The significantly higher risk of intracranial haemorrhage in this population and the lack of efficacy in the pediatric population tilts the balance significantly toward an adverse risk compared to any potential benefit ratio. Currently there is no evidence that it is beneficial in newborn infants. In the interim, focus should be on the prevention of sepsis with simple, cost effective and easy to practice established strategies like hand hygiene, strict adherence to sterile, aseptic techniques during procedures, early introduction of enteral feeding and optimal parenteral nutrition. Within the context of randomized controlled trials, the use of adjunctive treatments should still be explored and is justified in severe early onset sepsis and cases of nosocomial sepsis occurring in spite of preventive measures.

Addendum February 15, 2012

The first randomized controlled trial in adults, PROWESS, was stopped early for efficacy (Bernard 2001). Subsequently other studies like RESOLVE (Nadel 2007), ADDRESS (Abraham 2005) and ENHANCE (Goldstein 2006) did not show any efficacy and in fact the risk of bleeding was increased. A retrospective study in adults showed that the risk of serious bleeding was seen in 35% patients receiving rhAPC (Xigris®) compared to 3.8% (Gentry 2009). Due to numerous concerns being raised (Eichacker 2003; Sweeney 2009), a larger randomized controlled trial was planned with the study protocol well published prior to the conduct of the study (Finfer 2008; PROWESS SHOCK Steering Committee 2010; Ranieri 2011). This PROWESS-SHOCK clinical trial is yet to be published, but it failed to show a survival benefit. In this trial of 1696 patients, 851 patients were enrolled in the Xigris® arm and 845 patients were enrolled in the placebo arm. The preliminary analyses done by Eli Lilly, that were submitted to the FDA, showed a 28-day all cause mortality rate of 26.4% (223/846) in Xigris®-treated patients compared to 24.2% (202/834) in placebo-treated patients, for a relative risk of 1.09; 95% CI (0.92, 1.28), and P-value = 0.31 (not statistically significant) (FDA 2011a).

The FDA and European Medicines Agency (EMA) have now withdrawn their support and recommends not using the product

(FDA 2011b; European Medicines Agency (EMA) 2011) and the manufacturer has withdrawn the product from the market (Lilly 2011). All remaining rhAPC (Xigris) (drotAA) product should be returned to the supplier from whom it was purchased.

AUTHORS' CONCLUSIONS

Implications for practice

Despite the scientific rationale for its use, there is sufficient data to not use rhAPC for the management of severe sepsis in newborn infants. As the product has been withdrawn from the market due to lack of efficacy and higher risk of bleeding among adults receiving rhAPC (Xigris®) compared to the placebo group, it should not be used in neonates and no further trials are justified. There should be adequate emphasis on prevention of sepsis through simple, cost effective and proven measures like hand hygiene.

Implications for research

There is a need for adequately powered trials to determine the safety and efficacy of adjuvant therapy for severe neonatal sepsis. Researchers should be encouraged to initially undertake RCT's of different adjuvants in the treatment of confirmed or suspected severe neonatal sepsis in full term infants. If there is a minimal adverse effect profile and there are clinically significant outcomes, it would be justified to also study less severe forms of sepsis in full term infants and subsequently preterm and LBW infants, who have the highest risk of serious bleeding and intracranial haemorrhage. Researchers should be encouraged to report on clinically important co-morbidities of sepsis (e.g. chronic lung disease, periventricular leukomalacia, duration of assisted ventilation, necrotizing enterocolitis amongst others) and long term neurological outcome. Researchers might also compare different adjunctive treatments in addition to antimicrobials, such as early goal directed fluid resuscitation, tight glycaemic control, modulators of inflammation, immunomodulators, hematopoietic colony stimulating factors, anticoagulants or fibrinolytics among others in reducing mortality and morbidity due to severe neonatal sepsis.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Albuali 2005	Not a randomized controlled trial, single case report
Barton 2004	Not a randomized controlled trial, prospective no controls, no hard clinical endpoints, age: term newborn to < 18 years
Eli Lilly 2005a	Not a randomized controlled trial, No controls, prospective, paediatric data not published, Global ENHANCE, Term newborn to < 18 years
Eli Lilly 2005b	Randomized controlled trial, RESOLVE trial terminated and not published, > 38 weeks GA to < 18 years
Frommhold 2005	Not a randomized controlled trial; case report of a 12 day neonate with Gr B Strep sepsis
Lokeshwar 2006	Not a randomized controlled trial; report of two cases (5 months and 15 months old patients)
Manco-Johnson 2004	Not a randomized controlled trial; case report of use in 1 adolescent
Martinon-Torres 2004	Not a randomized controlled trial; case series of 3 children 1 -16 years
Nadel 2007	RESOLVE trial; randomized controlled trial terminated and not published, > 38 weeks GA to < 18 years
Rawicz 2002	Not a randomized controlled trial; case report of a newborn infant with early onset enterococcal sepsis
Sajan 2004	Not a randomized controlled trial; case report of a 4 month old infant with Serratia septic shock
Strohler 2004	Not a randomized controlled trial; case report of 35 week Gestational age 4 day infant with Gr B Strep sepsis
Verre 2005	Not a randomized controlled trial; single case report of a 7 year old
Wyss 2004	Not a randomized controlled trial; case series of 6 studies, newborn to < 18 years

APPENDICES

Appendix 1. Search Strategy - May 2011

PubMed:

(activated protein C OR Xigris OR Drotrecogin Alpha OR rhAPC) AND (sepsis OR septicemia OR septicaemia OR septic shock OR infection OR sepsis syndrome) AND ((infant, newborn[MeSH] OR newborn OR neon* OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW) AND (randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti])) NOT (animals [mh] NOT humans [mh])) AND (("2006"[Pdat] : "3000"[Pdat]))

Embase:

1 (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (607975)

- 2 (human not animal).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (11910500)
- 3 (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1266847)
- 4 ((activated protein C or Xigris or Drotrecogin Alpha or rhAPC) and (sepsis or septicemia or septicaemia or septic shock or infection or sepsis syndrome)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2005)
- 5 1 and 2 and 3 and 4 (23)
- 6 limit 5 to yr="2006 -Current" (17)

Cinahl:

((activated protein C OR Xigris OR Drotrecogin Alpha OR rhAPC) AND (sepsis OR septicemia OR septicaemia OR septic shock OR infection OR sepsis syndrome)) and ((infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial))

Limiters - Published Date from: 20060101-Present

Cochrane Central Register of Controlled Trials:

(infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)and (activated protein C OR Xigris OR Drotrecogin Alpha OR rhAPC) and (sepsis OR septicemia OR septicaemia OR septic shock OR infection OR sepsis syndrome), from 2006 to 2011

Clinicaltrials.gov

(infant OR newborn) AND (activated protein C OR Xigris OR Drotrecogin Alpha OR rhAPC) AND (sepsis OR septicemia OR septicaemia OR septic shock OR infection OR sepsis syndrome)

controlled-trials.com

(infant OR newborn) AND (activated protein C OR Xigris OR Drotrecogin Alpha OR rhAPC) AND (sepsis OR septicemia OR septicaemia OR septic shock OR infection OR sepsis syndrome)

WHAT'S NEW

Date	Event	Description
27 January 2020	Amended	Arne Ohlsson deceased.

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 2, 2006

Date	Event	Description
15 February 2012	New search has been performed	This review updates the existing review "Recombinant human activated protein C for severe sepsis in neonates" published in the Cochrane Database of Systematic Reviews (Kylat 2006). Search updated in May 2011.

Date	Event	Description
15 February 2012	New citation required and conclusions have changed	New references have been added to both excluded trials and additional references. In October 2011, rhAPC (Xigris®) was withdrawn from the market due to higher mortality in the rhAPC arm of a trial conducted in adults compared to the placebo arm. RhAPC should not be used in neonates and no further trials are recommended.
11 September 2008	Amended	Converted to new review format.
9 February 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Ranjit Kylat (RK) was involved in all stages of the review including registering the title, developing and writing the protocol, conducting the literature search, selecting the studies for inclusion/exclusion, developing data abstraction forms, assessing study quality, reviewing results and writing the text of the review. He contacted authors for additional data on published and unpublished trials.

Arne Ohlsson (AO) contributed to all stages of the review including refining the title, developing and writing the protocol, developing data abstraction forms, searching for articles, assessing study methodology and writing, revising and editing the text of the full review.

The July 2011 update was conducted centrally by the Cochrane Neonatal Review Group staff (Yolanda Montagne, Diane Haughton, and Roger Soll).

This update was reviewed and approved by RK and AO, who both wrote the addendum during the central review process.

DECLARATIONS OF INTEREST

None

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INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [therapeutic use]; Anti-Infective Agents [adverse effects] [*therapeutic use]; Chemotherapy, Adjuvant [methods]; Protein C [adverse effects] [*therapeutic use]; Recombinant Proteins [adverse effects] [therapeutic use]; Safety-Based Drug Withdrawals; Sepsis [*drug therapy] [mortality]

MeSH check words

Humans; Infant, Newborn