Cochrane Library

Cochrane Database of Systematic Reviews

Thrombolytic agents for arterial and venous thromboses in neonates (Review)

John CM, Harkensee C

John CM, Harkensee C.
Thrombolytic agents for arterial and venous thromboses in neonates.
Cochrane Database of Systematic Reviews 2005, Issue 1. Art. No.: CD004342.
DOI: 10.1002/14651858.CD004342.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Thrombolytic agents for arterial and venous thromboses in neonates

Cheri M John[1], Christian Harkensee[2]

[1]Paediatrics, Whiston Hospital, Prescot, UK. [2]Paediatrics, Newcastle General Hospital, Newcastle upon Tyne, UK

Contact: Cheri M John, Paediatrics, Whiston Hospital, Warrington Road, Prescot, L35 5DR, UK. cherijohn25@doctors.org.uk, cherijohn25@hotmail.com.

Editorial group: Cochrane Neonatal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: John CM, Harkensee C. Thrombolytic agents for arterial and venous thromboses in neonates. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD004342. DOI: 10.1002/14651858.CD004342.pub2.

ABSTRACT

Background

Clinically symptomatic thromboses are infrequent but serious complications in infants undergoing intensive care. Most are related to central vascular catheters. Symptomatic thrombosis may cause severe morbidity due to irreversible organ damage and also loss of limbs.

Objectives

To assess the efficacy and safety of thrombolytic agents in neonatal arterial and venous thromboses.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2004), MEDLINE (January 1966 to January 2004), EMBASE (January 1980 to January 2004), and CINAHL (January 1982 to January 2004). We also contacted authors of appropriate review articles.

Selection criteria

Randomised controlled trials (RCT) and quasi RCT comparing thrombolytic agents with either heparin or observation in neonates with symptomatic neonatal arterial and venous thromboses were included.

Data collection and analysis

Two reviewers independently searched for eligible trials. No eligible studies were found even after contacting authors of review articles for details of any unpublished trials.

Main results

No randomised controlled trials (RCT) or quasi-RCT were found.

Authors' conclusions

No conclusions could be made as no eligible studies were found. It is time that a randomised controlled trial was performed comparing thrombolytic therapy to heparin therapy to aid neonatologists in the treatment of arterial and venous thromboses.

PLAIN LANGUAGE SUMMARY

Thrombolytic agents for arterial and venous thromboses in neonates

Major blood clots are infrequent, but serious complications that can occur in neonatal intensive care. Most often, blood clots are related to catheters (thin tubes inserted into the body), especially those inserted into the torso, for instance umbilical catheters. These are used

in treating or monitoring sick newborn babies. Sometimes blood clots do not cause symptoms, but symptomatic blood clots can impair circulation and result in damage in the arms, legs, lungs, kidneys, heart, brain or intestines. The most common treatments are observation (no treatment), anti-clotting drugs (heparin), or clot-dissolving drugs (streptokinase, urokinase, and TPA). Surgery is also sometimes done. Administration of clot-dissolving drugs (thrombolytics) has a risk of causing severe bleeding. It is important to understand which treatment of blood clots produces the best short-term and long-term results. However, a search of the medical literature found no randomized clinical trials that compared clot-dissolving drugs with other blood clot treatments in newborns. Thus, no conclusions could be drawn.

BACKGROUND

Clinically symptomatic thromboses are infrequent but serious complications in neonates undergoing intensive care. Thromboses tend to occur in very sick neonates, particularly preterm neonates, and most are related to central vascular catheters. Furthermore, symptomatic thrombosis may result in death or severe morbidity due to irreversible organ damage. Incidence of symptomatic thrombosis is approximately 5.1 in 100,000 live births from the German Thrombosis Registry (Nowak-Gottl 1997), or approximately 1 case per centre per year in the Canadian Thrombosis Registry (Schmidt 1995). The incidence of asymptomatic thrombosis associated with indwelling catheters is probably much higher and has been estimated between 10 and 20 % (Horgan 1987; Olinsky 1975; Oppenheimer 1982; Seibert 1987).

Thrombotic disease may occur in any major blood vessel. The most common venous sites are the vena cava (superior and inferior, sometimes associated with renal vein thrombosis), the renal veins (associated with haematuria and enlarged kidneys), cerebral veins (associated with seizures), adrenal veins (associated with adrenal haemorrhage and necrosis), and the portal and hepatic veins. Of the arteries the most commonly affected are the aorta (associated with congestive heart failure, systolic gradient between upper and lower limbs, and decreased femoral pulses), peripheral limb (associated with local ischaemic signs), cerebral (associated with apnoeas and seizures), pulmonary (associated with respiratory distress and pulmonary hypertension), coronary (associated with cardiac ischaemia), renal (associated with systemic hypertension, or congestive cardiac failure) and mesenteric (associated with signs of necrotizing enterocolitis) (Schmidt 1984; Edstrom 2000). Risk factors, in addition to indwelling catheters, include high haematocrit, increased plasma viscosity, disseminated intravascular coagulation, infants of diabetic mothers, sepsis, small for gestational age babies, congenital heart disease, maternal antiphospholipid syndrome and inherited prothrombotic disorders such as Protein C or Protein S deficiency (Edstrom 2000).

Invasive procedures such as venous and arterial umbilical catheters, central venous lines and peripheral arterial and venous access may cause thrombo-embolic disease by damaging the vessel wall endothelium, and introducing a potentially thrombogenic surface into the vessel. Thrombus formation in the neonate is most commonly a result of an activated functioning coagulation cascade. Activation of the extrinsic (tissue lesion) or intrinsic pathway (intravascular induction) results in precipitation of fibrin at the site of the lesion. Thrombocytes adhere to and fibroblasts migrate into the initial clot, which constricts by interlinking fibrin molecules.

D-dimers are not particularly useful in diagnosis of thrombosis as there appears to be a wide range of levels in apparently normal infants (Hudson 1990). Contrast angiography gives the most accurate diagnosis but is invasive (Manco-Johnson 1990; Olinsky 1975) . Realtime ultrasonography and Doppler studies are good adjunctive measures, but their precision and accuracy in neonatal thrombotic disease are still uncertain (Schmidt 1988).

Observation, standard heparin, low molecular weight heparin, thrombolysis, and on occasions, surgical intervention are the available and most commonly used treatment options (Edstrom 2000). Streptokinase and urokinase (non-fibrin specific plasminogen activators) and recombinant tissue plasminogen activator (rTPA) have all been used for symptomatic thrombosis in neonates. Urokinase (a plasminogen activating human enzyme, derived from urine) has a better safety profile compared to streptokinase (a toxin of haemolytic group C streptococcus). TPA is a fibrin-specific human tissue protein which promotes the transformation of plasminogen into plasmin, a proteolytic enzyme which directly digests fibrin and clotting factors (Martindale, 1999). Contraindications follow mainly adult practice: recent or ongoing haemorrhage (in particular intracranial or pulmonary haemorrhage), coagulation defects and bleeding diatheses, peptic ulceration, severe liver disease, recent trauma or surgery. The main complication of administration of thrombolytic agents in neonates as in adults is induction of severe haemorrhage. Reported sites of bleeding include local puncture sites or recent catheterisation sites (10.4%), pulmonary haemorrhage (0.6%), gastro-intestinal haemorrhage (0.6%) and intraventricular haemorrhage (2.7%). Only two of a series of 182 infants who received thrombolytic therapy died from a resulting haemorrhage (Nowak-Gottl 1999).

Data on long-term follow up of neonatal thrombosis are limited. Follow-up data on aortic thrombosis suggest that persistent hypertension, leg-growth discrepancy and renal dysfunction may occur (Caplan 1989; Payne 1989; Seibert 1991). Heparin infused in low dose (< 200 units/kg/day) via an umbilical artery catheter prolongs the patency of the catheter (Rajani 1979; David 1981; Bosque 1986; Horgan 1987). However, there are no data available so far to show whether continuous low dose heparin via umbilical artery catheters reduces catheter-associated thrombus formation.

OBJECTIVES

The primary objective was to assess effectiveness and safety of thrombolytic agents (streptokinase, urokinase or rTPA) for the treatment of clinically manifest arterial or venous thrombosis in newborn infants. We aimed to assess the results of various treatment regimens. In separate comparisons, we planned to compare thrombolytic agents with either no treatment, heparin, or surgery, each used as primary treatment. Secondary objectives were to conduct subgroup analyses within each comparison, in which we planned to assess treatment effects on arterial or venous thromboses; and according to the specific thrombolytic agent tested: streptokinase, urokinase or rTPA.

We aimed to specifically test the following hypothesis: thrombolytic agents to treat symptomatic arterial or venous thrombosis are effective in preventing complications including limb or organ ischaemia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised controlled trials

Types of participants

Neonates (up to 28 days old) with symptomatic arterial or venous thrombosis.

Types of interventions

Studies which compared a thrombolytic agent (streptokinase, urokinase, rTPA, any dose eligible) with either no treatment, heparin, or surgery (each used as primary treatment). Studies which allowed surgery as back-up after failed primary treatment were eligible. Studies which compared different doses of a thrombolytic agent were eligible. Studies using heparin alone as a therapeutic intervention were not eligible as heparin is not a thrombolytic agent.

Types of outcome measures

PRIMARY OUTCOMES

1. Failure of reperfusion of an affected limb clinically (failure of capillary refill time to return to two seconds, failure of normalisation of kidney or liver function, failure of blood pressure to normalise)
2. Failure of resolution of the thrombus on imaging

SECONDARY OUTCOMES

1. Failure of the platelet count to stabilise.
2. Side effects: hypersensitivity and hypotension
3. Complications: haemorrhage (intraventricular haemorrhage, bleeding from venepuncture or arterial puncture sites, haematuria, gastro-intestinal bleeding) and secondary emboli due to broken down and dislodged clots.
4. Mortality within a week of intervention

Search methods for identification of studies

Relevant trials (RCTs and quasi-RCTs) in all languages were collected by searching the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2004), MEDLINE (1966-2003), EMBASE (1980-2003), CINAHL (1982-2003), The Royal Pharmaceutical Society Databases (ePic, Ceuted, New Products, Discontinued Products) in the 2003 version, HMIC:DH Data and King's Fund Database 2003/1, Serfile 2002 version. We used at first level the individual search terms "neonate" (plus: "neonat*"), "thrombosis" (plus: "thrombos*"), "clot", "blood clot", "thrombolysis" (plus: "thromboly*"), "fibrinolysis" (plus: "fibrinoly*), "Urokinase", "Streptokinase", "recombinant tissue plasminogen activator" (plus: "rTPA"). We then carried out combined searches combining "neonate" (plus: "neonat*") individually with all other search terms.

Data collection and analysis

The two reviewers (CJ and CH) independently planned to select the trials to be included in the review. The methodological quality of each trial was to be assessed by each reviewer. In particular, reviewers planned to examine details of the randomisation method, whether the trial was blinded, 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 was recorded. Data were to be independently extracted by each reviewer using standard data acquisition forms. If disagreement arose on the suitability of a trial for inclusion in the review or on its quality, we planned to attempt to reach a consensus by discussion. We planned to rate each of the four elements of methodological quality used by the Cochrane Neonatal Review Group. We planned to rate blinding of randomisation, blinding of intervention, completeness of follow-up, and blinding of outcome assessments (as yes/no/can't tell).

For binary outcome measures, data on the number of patients with each outcome event, by allocated treated group, irrespective of compliance and whether or not the patient was later thought to be ineligible or otherwise excluded from treatment or follow-up were to be sought to allow an intention-to-treat analysis. Treatment effect was planned to be analysed using relative risk and risk differences for binary outcomes and either mean and standard deviation for change from baseline for each group or mean post-treatment/intervention values and standard deviation for each group for continuous outcomes. We planned to pool trials for meta-analyses if appropriate. For meta-analyses, a fixed effect model was to be assumed. A pooled estimate of treatment effect for each outcome across studies was planned to be calculated as typical relative risk and typical risk differences for binary outcomes, and weighted mean differences for continuous outcomes. 95% confidence intervals were to be used for each measure of treatment effect. Heterogeneity between trial results was to be tested for using a standard chi-squared test or ANOVA as appropriate. We planned to perform a sensitivity analysis based on the methodological quality of the studies, including and excluding quasi-randomised studies.

RESULTS

Description of studies

No randomised controlled trials (RCT) or quasi RCTs were found

Risk of bias in included studies

Not applicable as no eligible studies were found.

Effects of interventions

No results were forthcoming as no eligible studies were found.

DISCUSSION

We found seven studies which were potentially eligible. There were two RCTs of low molecular weight heparin for treatment or prevention of thrombosis in children (Massicotte 2003a; Massicotte 2003b). However, they were not eligible as heparin is not a thrombolytic agent.

In another clinical trial (Wang 2003), there were only eight neonates in the study forming a very heterogenous group. The study was neither randomised nor controlled. The authors themselves state that their study cannot form the basis for treatment recommendations.

A study on 76 very low birth weight infants with umbilical catheters in situ showed that four patients had intracardiac thromboses which resolved with an infusion of r-TPA with no systemic side effects observed (Ferrari 2001). However, the study was not randomised.

A study on the efficacy and safety of r-TPA in 17 children and adolescents with arterial and venous thromboses of varying causes demonstrated complete re-perfusion in 13 patients and partial re-perfusion in two patients. There were no serious side effects in the neonates in the study which numbered only two (Nowak-Gottl 1991)

Four neonates with caval thrombosis secondary to indwelling central catheters were given r-TPA as a low-dose infusion (0.05 mg/kg/h) directly into the thrombus. Thrombolysis was successful in 3 patients and one neonate suffered an intracranial haemorrhage. This study was not randomised or controlled (Anderson 1991).

In a prospective cohort study (Cheah 2001) of 31 neonates with umbilical catheter associated thrombi, 22 had successful thrombolysis with low dose streptokinase (1000 units/h) after a mean interval of 2.2 days. Only one infant developed mild bleeding attributed to streptokinase therapy. This study was not randomised.

We contacted two investigators in the field. Dr Barbara Schmidt who is the author of a major survey of the use of thrombolytic agents was contacted in January 2004 and she was unaware of any unpublished or ongoing trials. Dr U Nowak-Gottl, who is the author of a similar survey of the use of thrombolytic agents in neonates, was contacted in December 2003 and she was unaware of any unpublished or ongoing trials.

AUTHORS' CONCLUSIONS

Implications for practice

No conclusions could be made

Implications for research

There is a need for adequately powered muticentre trials to determine the safety and efficacy of thrombolytic therapy for major thromboses in the neonate. Such trials may have to be conducted on a mutinational basis because of the rarity of this condition. It is time that a randomised controlled trial was performed comparing thrombolytic therapy with heparin therapy to aid neonatologists in the treatment of this rare but potentially fatal condition.

ACKNOWLEDGEMENTS

We wish to thank Professor Henry Halliday and Dr. David Milligan for their advice and support. We wish to thank Professor Jim Neilson for generic advice on completing the review.

REFERENCES

References to studies excluded from this review

Anderson 1991 *{published data only}*

Anderson BJ, Keeley SR, Johnson ND. Caval thrombolysis in neonates using low doses of recombinant human tissue plasminogen activator. *Anaesthia and Intensive Care* 1991;**19**:22-7.

Cheah 2001 *{published data only}*

Cheah FC, Boo NY, Rohana J, Yong SC. Successful clot lysis using low dose of Streptokinase in 22 neonates with aortic thromboses. *Journal of Paediatrics and Child Health* 2001;**37**:479-82.

Ferrari 2001 *{published data only}*

Ferrari F, Vagnarelli F, Gargano G, Roversi MF, Biagioni O, Ranzi A, Cavazzuti GB. Early intra-cardiac thrombosis in preterm infants and thrombolysis with recombinant tissue type plasminogen activator. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2001;**85**:F66-9.

Massicotte 2003a *{published data only}*

Massicotte P, Julian JA, Gent M, Shields K, Marzinotto V, Szechtman B, et al. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. *Thrombosis Research* 2003;**109**:85-92.

Massicotte 2003b *{published data only}*

Massicotte P, Julian JA, Gent M, Shields K, Marzinotto V, Szechtman B. An open-label randomized controlled trial of low molecular weight heparin for the prevention of central venous line-related thrombotic complications in children: the PROTEKT trial. *Thrombosis Research* 2003;**109**:101-8.

Nowak-Gottl 1991 *{published data only}*

Nowak-Gottl U, Kreuz WD, Schwabe D, et al. Thrombolysis with r-TPA in children suffering from arterial or venous thromboses [Thrombolyse mit rTPA bei Kindern mit arteriellen und venosen Thrombosen]. *Klinische Padiatrie* 1991;**203**:359-62.

Wang 2003 *{published data only}*

Wang M, Hays T, Balasa V, Bagatell R, Gruppo R, Grabowski EF, et al. Low-dose tissue plasminogen activator thrombolysis in children. *Journal of Pediatric Hematology/Oncology* 2003;**25**:379-86.

Additional references

Andrew 2001

Andrew ME, Monagle P, de Veber G, Chan AK. Thromboembolic disease and antithrombotic therapy in newborns. *Hematology (Am Soc Hematol Educ Program)* 2001:358-74.

Blanchette 1994

Blanchette V, Doyle J, Schmidt B, et al. Neonatal thrombosis and emboli. Pathophysiology and management of the newborn. Edited by Avery, Fletcher and Macdonald. 1994. Philadelphia: JB Lippincott, 1994.

Bosque 1986

Bosque E, Weaver L. Continuous versus intermittent heparin infusion of umbilical artery catheters in the newborn infant. *Journal of Pediatrics* 1986;**108**:141-3.

Caplan 1989

Caplan MS, Cohn RA, Langman CB, Conway JA, Shkolnik A, Brouillette RT. Favorable outcome of neonatal aortic thrombosis and renovascular hypertension. *Journal of Pediatrics* 1989;**115**:291-5.

David 1981

David RJ, Merten DF, Anderson JC, Gross S. Prevention of umbilical artery catheter clots with heparinized infusates. *Developmental Pharmacology and Therapeutics* 1981;**2**:117-26.

Edstrom 2000

Edstrom CS, Christensen RD. Evaluation and treatment of thrombosis in the neonatal intensive care unit. *Clin Perinatol* 2000;**27**:623-41.

Horgan 1987

Horgan MJ, Bartoletti A, Polansky S, Peters JC, Manning TJ, Lamont BM. Effect of heparin infusates in arterial umbilical artery catheters on frequency of thrombotic complications. *Journal of Pediatrics* 1987;**111**:774-8.

Hudson 1990

Hudson IRB, Gibson BES, Brownlie J, Holland BM, Turner TL, Webber RG. Increased concentration of D-dimers in newborn infants. *Archivs of Disease in Childhood* 1990;**65**:383-4.

Manco-Johnson 1990

Manco-Johnson M. Diagnosis and management of thromboses in the perinatal period. *Seminars in Perinatology* 1990;**14**:393-402.

Martindale, 1999

Martindale. The complete drug reference. 2nd Edition. Vol. **1**, Pharmaceutical Press, 1999.

Nowak-Gottl 1997

Nowak-Gottl U, von Kries R, Gobel U. Neonatal symptomatic thrombo-embolism in Germany: two year survey. *Arch Dis Child Fetal Neonatal Ed* 1997;**76**:F163-7.

Nowak-Gottl 1999

Nowak-Gottl U, Auberger K, Halimeh S, Junker R, Klinge J, Kreuz WD, et al. Thrombolysis in newborns and infants. *Journal of Thrombosis and Haemostasis* 1999;**82**:112-6.

Olinsky 1975

Olinsky A, Aitken FG, Isdale, JM. Thrombus formation after umbilical arterial catheterisation. An angiographic study. *South African Medical Journal* 1975;**49**:1467-70.

Oppenheimer 1982

Oppenheimer DA, Carroll BA, Garth KE. Ultrasonic detection of complications following umbilical arterial catheterization in the neonate. *Radiology* 1982;**145**:667-72.

Payne 1989

Payne RM, Martin TC, Bower RJ, Carter CE. Management and follow-up of arterial thrombosis in the neonatal period. *Journal of Pediatrics* 1989;**114**:853-8.

Rajani 1979

Rajani K, Goetzman BW, Wennberg RP, Turner E, Abildgaard C. Effect of heparinization of fluids infused through an umbilical artery catheter on catheter patency and frequency of complications. *Pediatrics* 1979;**63**:552-6.

Schmidt 1984

Schmidt B, Zipursky A. Thrombotic disease in newborn infants. *Clinics in Perinatology* 1984;**11**:461-88.

Schmidt 1988

Schmidt B, Andrew M. Neonatal thrombotic disease - prevention, diagnosis and treatment. *Journal of Pediatrics* 1988;**113**:407-10.

Schmidt 1995

Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics* 1995;**96**:939-43.

Seibert 1987

Seibert JJ, Taylor BJ, Williamson L, Williams BJ, Szabo JS, Corbitt SL. Sonographic detection of neonatal umbilical artery thrombosis: clinical correlation. *American Journal of Roentgenology* 1987;**148**:965-8.

Seibert 1991

Seibert JJ, Northington, FJ, Miers JF, Taylor BJ. Aortic thrombosis after umbilical artery catheterisation in neonates: prevalence of complications on long-term follow-up. *American Journal of Roentgenology* 1991;**156**:567-9.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anderson 1991	The study was neither randomised nor controlled.
Cheah 2001	This was a prospective cohort study and the patients were neither randomised nor controlled.
Ferrari 2001	The study was neither randomised nor controlled.
Massicotte 2003a	Heparin is not a thrombolytic agent and the study is therefore ineligible.
Massicotte 2003b	Heparin is not a thrombolytic agent and the study is therefore ineligible.
Nowak-Gottl 1991	The study was neither randomised or controlled. Only 17 subjects in the study including children and adolescents, of which there were only two neonates
Wang 2003	A very heterogenous group with only eight neonates in the study. The study in itself is neither randomised nor controlled.

WHAT'S NEW

Date	Event	Description
22 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Both the reviewers conceived, designed and co-ordinated the review. We developed the search strategy, undertook searches, screened the search results and wrote to authors of papers for information on any unpublished trials. Both of us entered the data onto RevMan. We have provided a methodological, clinical, policy and consumer perspective.

DECLARATIONS OF INTEREST

None

INDEX TERMS

Medical Subject Headings (MeSH)

*Thrombolytic Therapy; Arteries; Fibrinolytic Agents [*therapeutic use]; Thrombosis [*drug therapy]; Venous Thrombosis [drug therapy]

MeSH check words

Humans; Infant, Newborn