Tranexamic acid in the prevention of periventricular haemorrhage

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SUMMARY  Increased fibrinolytic activity in the ganglionic eminence of the preterm human brain has been proposed as a factor in the aetiology of periventricular haemorrhage. The effect of tranexamic acid in preventing periventricular haemorrhage was evaluated in 100 infants in a double blind, randomised controlled trial. Haemorrhages developed in 22 infants who received tranexamic acid and in 20 of those who received placebo. A significant reduction in fibrin degradation products in treated infants was seen. Our study suggests that excessive fibrinolytic activity is not an important factor in the aetiology of periventricular haemorrhage and that treatment with tranexamic acid will not prevent its occurrence.

Periventricular haemorrhage is a major cause of mortality and morbidity in the neonatal intensive care unit. Using non-invasive diagnostic techniques, it has been found in 40 to 50% of very low birthweight infants, and the incidence is highest among infants born at less than 32 weeks' gestation. Anatomical studies have shown that the common site of origin of periventricular haemorrhage is the vessels of the germinal matrix capillary bed. The extensive spread of capillary haemorrhage in the germinal matrix may be explained by the increased fibrinolytic activity described in this area.

The prevention of periventricular haemorrhage is multifactorial in approach, and drugs may have a part to play. Ethamsylate has been used and shown, in a controlled trial, to reduce the incidence of haemorrhage. Phenobarbitone has shown to be effective but considerable disagreement exists over its effectiveness. Tranexamic acid is an inhibitor of plasminogen activators that have fibrinolytic properties, and it has been shown to reduce the measured fibrinolytic activity of germinal matrix extracts when used in vitro. In the newborn, it has been used in uncontrolled trials. We have conducted a randomised, double blind controlled trial using tranexamic acid to investigate its effectiveness in preventing periventricular haemorrhage.

Patients and methods

All infants weighing less than 1250 g at birth and those infants weighing less than 1500 g who required respiratory support in the first day of life were enrolled in the study after their admission to this neonatal intensive care unit. One hundred patients entered the trial during a 14 month period. Both inborn and outborn patients were eligible for inclusion but infants transferred to the unit after 24 hours of age were excluded from the study, as were those with chromosomal abnormalities and lethal congenital anomalies.

Tranexamic acid (Cyklokapron) (100 mg/ml) or placebo was provided by the manufacturer (Kabi-Vitrum) in 100 numbered batches containing 20 vials. The randomised code was held by the manufacturers until the end of the trial. Infants received 0.25 ml/kg of drug or placebo intravenously six hourly for five days. Blood was collected daily for full blood count, platelets, prothrombin time, partial thromboplastin time, fibrin degradation products, creatinine, and plasma electrolyte determinations. Most of these investigations formed part of daily intensive care requirements. If there was evidence of disseminated intravascular coagulopathy treatment was stopped, and if the serum creatinine concentration exceeded 120 μmol/l the frequency of dosage was reduced to 12 hourly.

Ultrasound scanning of the head through the anterior fontanelle was carried out before the first dose of trial drug, daily for the first 7 days of life, and weekly thereafter. An ATL (Advanced Technology Laboratories Inc) mechanical sector scanner with 5 MHz transducer was used. Parasagittal and
coronal views were examined and recorded on polaroid film. Ultrasound appearances of periventricular haemorrhage were graded 1 to 4 in a way similar to that described by Papile et al. Clinical data relating to factors known to be associated with the occurrence of periventricular haemorrhage were recorded.

Approval for the trial was given by the hospital ethical committee.

Results

One hundred infants were entered into the trial. Treatment with the trial drug was stopped in two infants because of the development of disseminated intravascular coagulation on their second day; one had received tranexamic acid and the other placebo. There were no significant differences between the tranexamic acid group and placebo group in birthweight, gestational age, and other clinical factors which may be related to the development of periventricular haemorrhage (Table 1).

Periventricular haemorrhages developed in 22 infants in the treated group and 20 in the placebo group. The mean time of detection of haemorrhage in both groups was 48 hours. The severity of haemorrhage did not differ significantly between groups (Table 2). Five infants who had periventricular haemorrhages developed serious hydrocephalus which was controlled by insertion of a ventriculoperitoneal shunt. Two were in the tranexamic acid group and three in the placebo group. More infants died in the tranexamic acid group, although the difference was not statistically significant.

Infants receiving tranexamic acid had significantly lower fibrin degradation products measured during the period they were receiving the drug (days 1 to 5) compared with the placebo group (Table 3). The prothrombin time, partial thromboplastin time, and platelet counts did not differ significantly in the two groups. There were no differences in the measured fibrin degradation product values at any time during the trial when those in the tranexamic acid group who had a haemorrhage were compared with those in the same group whose ultrasound scans remained clear.

Discussion

Tranexamic acid is a water soluble compound (trans-4-(aminomethyl) cyclohexene carboxylic acid) which is absorbed and excreted unchanged. It is less toxic and seven to 10 times more potent than aminocaproic acid. It is an antifibrinolytic agent which competitively inhibits the activation of plasminogen to plasmin. Tranexamic acid has been shown to reduce the incidence of recurrent haemorrhage after initial subarachnoid haemorrhage in adults. When given to 100 pregnant women at term there was no difference in the incidence of retinal haemorrhage 24 hours after birth in infants in the treated group compared with the infants of 100 controls. It has also been given to asphyxiated infants with haemorrhagic disorders.

Toxic effects of tranexamic acid are generally mild; these are limited to gastrointestinal disturbances when given orally and hypotension on rapid intravenous injection. Cerebral ischaemia has been noted in a series when tranexamic acid was given after subarachnoid haemorrhage. This has not
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been confirmed. As tranexamic acid will reduce natural reabsorption of intravascular clots once formed, there is a theoretical possibility that there will be an increased incidence of hydrocephalus in patients. In adult patients, however, given tranexamic acid for four weeks after subarachnoid haemorrhage, there was no increase in the incidence of hydrocephalus in treated as against control groups.

Periventricular haemorrhage in the preterm low birthweight infant arises from the poorly supported capillaries in the subependymal germinal matrix. Homogenates of haemorrhage-free germinal matrix preparations have shown the presence of fibrinolytic activity. The activity decreased as gestational age increased. As tranexamic acid inhibited the measured fibrinolysis it was postulated that the active extract was a plasminogen activator. It has been suggested and widely accepted that a similar mechanism is active in vivo explaining the extensive spread of periventricular haemorrhage from its capillary origins. It is reasonable to expect, therefore, that tranexamic acid would reduce the incidence or severity of periventricular haemorrhage, or both, when used in very low birthweight infants.

In this study, there was no difference in the incidence of periventricular haemorrhage in the tranexamic acid treated and control groups. The extent of the bleed did not differ significantly in either group, although there was a trend for intraventricular (grade 2) and parenchymal haemorrhages (grade 4) to be more common in the treated group. This is not what one would expect when fibrinolysis is inhibited. In treated patients the concentration of serum fibrin degradation products during the period of treatment was lower than in those infants receiving placebo, indicating that tranexamic acid was inhibiting fibrinolysis. Complications attributable to the use of tranexamic acid were not observed. Although five infants developed hydrocephalus which required treatment with a ventriculoperitoneal shunt, three of these infants were in the placebo group. The pathogenesis of periventricular haemorrhage is related to several factors concerned with the regulation and distribution of cerebral blood flow, intravascular pressure, capillary stability, and the extravascular environment. Although increased fibrinolysis has been shown in the germinal matrix of preterm infants, and in vitro this may be inhibited by tranexamic acid, our study suggests that this mechanism is not important in the pathogenesis of periventricular haemorrhage. Tranexamic acid does not have a role in the prevention of periventricular haemorrhage in the very low birthweight infant.

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References


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