Trasylol in Cases of Accidental Haemorrhage with Coagulation Disorder and Associated Uterine Inertia

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SUMMARY

Nine cases of severe accidental haemorrhage with coagulation defects are discussed with special reference to uterine inertia. It is suggested that Trasylol may play a specific role in reversing uterine inertia. The mechanism of this is discussed.

It is further suggested that heparin may potentiate its activity.

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In most cases of accidental haemorrhage, the first stage of labour is shortened.[1] However, in a small number of cases, the obstetrician is called upon to make the unpleasant decision of whether or not he should resort to an abdominal delivery because of uterine inertia. Inertia is a rare complication of accidental haemorrhage, but when it does occur it is in those cases where a coagulation disorder has developed. In such cases the fetus is usually already dead and the dangers of Caesarean section are greatly increased because of an associated coagulation disorder which may at the time have been only partially corrected.

This retrospective study evaluates the relationship between uterine activity and methods of management in cases of severe accidental haemorrhage with associated coagulation disorder. It was embarked upon in an attempt to determine whether management had any effect upon uterine activity in such cases.

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PATIENTS AND METHODS

The 9 cases described below include all the cases of accidental haemorrhage with associated coagulopathy seen in the Groote Schuur Hospital Maternity Unit from 1 July 1971 to 31 August 1973. During this period 116 cases of accidental haemorrhage were admitted (10,4%).

A diagnosis of a coagulopathy was made on the basis of the following observations:

(a) prolonged coagulation time (more than 10 minutes) performed in a standard manner at 37°C.

(b) prolonged bleeding time (more than 10 minutes) performed in a standard manner at 37°C;

(d) lysis of donor blood clot by the patient's serum at 37°C;

(e) the Fi-test for estimation of fibrinogen and fibrin degradation product levels (FDP);

(f) the microscopic examination of a blood smear for platelets.

The existence of a significant degree of fibrinolysis was diagnosed by means of (*c*), (*d*) and (*e*). Haematological confirmation of the diagnosis was obtained in 4 of the 9 cases.

Case 1

The patient was 23 years old; para 1; gravida 2; and the gestational age on admission was 37 weeks.

She had attended antenatal clinic once only, prior to her emergency admission. She was shocked on arrival and had felt no fetal movement for 9 hours. The features of a classic accidental haemorrhage with fetal death were present and a severe coagulation disorder with fibrinolysis was diagnosed. The plasma fibrinogen level was 57 mg/100 ml. The level of fibrin degradation products (FDP) was more than 160 µg/ml and the platelet count was 63 000/min. Fresh blood, fibrinogen and platelets were administered and the central venous pressure and urine output monitored.

A vaginal examination revealed a cephalic presentation and the cervix was uneffaced and 1 cm dilated. An artificial rupture of membranes produced heavily blood-stained liquor amnii, and an oxytocin infusion was commenced. Vaginal examinations were done every 4 hours, and after 12 hours no cervical change was detected.

At this stage the oxytocin infusion was discontinued and 500 000 units of Trasylol plus 10 000 units of heparin were administered intravenously. Four hours later the cervix was 5 cm dilated and fully effaced. One-and-a-half hours later, the patient gave birth to a 2 700-g, fresh stillborn baby. There was 1 200 ml retroplacental clot. The postpartum uterus remained well contracted and no significant haemorrhage occurred. A total of 6 g of fibrinogen, 9 units of whole blood, and 3 units of platelet concentrate had been administered to this patient.

Case 2

The patient was 36 years old; para 8, gravida 9; and the gestational age was 32 weeks. She had attended the antenatal clinic regularly, the only feature of note having been poor weight gain. She was admitted in a state of shock with classic features of a severe accidental haemorrhage. On admission the fetal heart rate was 100/minute but this soon disappeared. A severe coagulation disorder with associated fibrinolysis was diagnosed. The plasma fibrinogen level was 20 mg/100 ml, and the level of FDP was more than 160 µg/ml. Whole blood and fibrinogen were administered.

A vaginal examination revealed a cephalic presentation and the cervix was 2 cm dilated and uneffaced. An artificial rupture of membranes was performed and an oxytocin infusion commenced. After 12 hours there was no detectable cervical change and 500 000 units of Trasylol were administered intravenously with 10 000 units of heparin.

Four-and-three-quarter hours later, the patient gave birth to a stillborn infant weighing 1 950 g. There was 2 000 ml of retroplacental clot. The uterus remained well contracted after delivery and no postpartum haemorrhage occurred. The patient had received 4 units of whole blood, 4 g of fibrinogen and 3 units of fresh frozen plasma.

Case 3

The patient was 23 years old; para 3, gravida 4; and the gestational age was 34 weeks. She had attended the antenatal clinic regularly. On admission she was shocked and gave a history of vague abdominal pain and bleeding which had commenced three hours before admission. The fetal heart rate was 80/minute but disappeared within 15 minutes. The presence of a coagulation defect with fibrinolysis was noted. Whole blood was administered and the central venous pressure and urine output monitored.

A vaginal examination revealed a cephalic presentation and the cervix was 2 cm dilated and uneffaced. An artificial rupture of membranes was performed and an oxytocin infusion was commenced. After 8 hours and with no change detectable at a cervical level, Trasylol 500 000 units and heparin 10 000 units were administered intravenously. Delivery of a stillborn baby weighing 1 950 g was effected 5 hours later. There was 1 000 ml of retroplacental clot. Delivery was followed by a postpartum haemorrhage of 900 ml due to a cervical laceration. This was sutured and the bleeding controlled. A total of 6 units of whole blood had been administered.

Case 4

The patient was 20 years old; para 1; gravida 2; and the gestational age was 32 weeks. She was admitted in a state of coma, having experienced 3 eclamptic convulsions over a period of 5 hours.

Examination revealed signs of accidental haemorrhage with no audible fetal heart. A coagulation disorder was diagnosed. Clot lysis was strongly positive and FDP level was more than 160 µg/ml and the plasma fibrinogen level 42 mg/100 ml. It became evident that the patient had developed an intracranial haemorrhage as well. The presence of blood-stained and xanthochromic cerebrospinal fluid confirmed this. A regimen of restoring blood coagulability with fresh whole blood fibrinogen and fresh frozen plasma was commenced and the central venous pressure monitored.

On vaginal examination the cervix was found 3 cm dilated and partially effaced. A forewater rupture of the membranes was performed, and an oxytocin infusion commenced. After 10 hours the cervix was still 3 cm dilated but almost completely effaced. Trasylol 500 000 units was administered intravenously and 6 hours later the patient was delivered of a 1 400 g stillborn baby and 1 200 ml of retroplacental clot. The uterus contracted well postpartum and no significant degree of haemorrhage occurred. A total of 6 units of whole blood, 4 units of fibrinogen and 3 units of fresh frozen plasma had been administered.

The patient regained consciousness and an angiogram confirmed intracranial haemorrhage. She improved at first, and except for a residual left hemiparesis and a mild aphasia, was well. On the second postpartum day she deteriorated rapidly and died from a repeat massive intracranial haemorrhage.

Case 5

The patient was 38 years old; para 6; gravida 7; and gestational age was 37 weeks.

This emergency case gave a past history of an accidental haemorrhage with her previous pregnancy. She was admitted in a state of shock, and although all the abdominal findings of a classic accidental haemorrhage with intra-uterine death were noted, there was no vaginal bleeding. A coagulation disorder with fibrinolysis was noted. The plasma fibrinogen level was 71 mg/100 ml and the platelet count 69 000/mm^2. Fibrinogen and whole blood were administered and the central venous pressure monitored.

The cervix was found to be 3 cm dilated and partially effaced. Nine hours later no cervical change was detected. The coagulation time was then 8 minutes and a Caesarean section was performed. Uterine haemorrhage at operation required rapid transfusion of whole blood and fibrinogen. The presence of a Couvelaire uterus was noted. The stillborn baby weighed 2 750 g, had a meningocele and a spina bifida, and there was

2 000 ml of retroplacental clot. There was still difficulty in getting this uterus to contract and postpartum haemorrhage necessitated the infusion of large doses of oxytocin. The patient receivevd a total of 6 units of whole blood and 4 g of fibrinogen.

Case 6

This patient was 20 years of age; para 2; gravida 3; and the gestational age was 36 weeks. She had never attended antenatal clinic and was in a state of shock with a classic accidental haemorrhage. No fetal heart was detectable and a severe coagulation disorder with fibrinolysis was diagnosed. She was resuscitated with whole blood. The cervix was 2 cm dilated and uneffaced and the presentation cephalic. An artificial rupture of membranes produced heavily blood-stained liquor amnii and an oxytocin infusion was commenced.

After 12 hours and no cervical change, the patient received more fibrinogen and a Caesarean section was performed. The stillborn fetus weighed 2 700 g and there was more than 1 000 ml of retroplacental clot. There was no postpartum haemorrhage. The patient had received 4 units of whole blood and 4 g of fibrinogen.

Case 7

This patient was 35 years old; para 4; gravida 5; and the gestational age was 42 weeks. She had attended the antenatal clinic regularly, and was admitted with a mixed accidental haemorrhage and not in shock. Fetal movement had not been felt by the patient for 10 hours and no fetal heart was heard. A coagulation disorder with fibrinolysis was diagnosed.

On vaginal examination the cervix was undilated, fully effaced and the presentation was cephalic. A forewater rupture of membranes was performed and an oxytocin infusion commenced. Blood, fresh frozen plasma and fibrinogen were administered, and the central venous pressure was monitored. Ten thousand units of heparin were administered intravenously. Eight hours later, after no cervical change was detected, the effect of heparin was reversed with protamine sulphate, and Trasylol 500 000 units and 4 g of fibrinogen were given intravenously. A Caesarean section was performed. The fresh stillborn baby weighed 3 600 g and there was 1 500 ml of retroplacental clot. The presence of a Couvelaire uterus with bilateral broad ligament haematomas was observed. A total of 4 units of blood, 4 g of fibrinogen and 2 units of fresh plasma had been administered. No postpartum haemorrhage occurred, and the uterus remained well contracted.

Case 8

The patient was aged 18 years; para 0; gravida 1; and the gestational age was 34 weeks. She was admitted as an emergency case suspected of having a placenta praevia. The fetal heart was audible at 144/minute. During the investigation the classic features of a severe accidental haemorrhage developed and the fetal heart sounds disappeared. A severe coagulation disorder with fibrinolysis developed.

On vaginal examination the cervix was found to be 9 cm dilated. After artificial rupture of membranes and oxytocin infusion the patient gave birth to a 2 000 g stillborn baby. There was 2 000 ml of retroplacental clot.

After delivery the patient had a massive postpartum haemorrhage and collapsed. Despite the administration of large doses of oxytocin and syntometrine, the uterus remained atonic. Epsilon-aminocaproic acid was administered and the uterus regained its tone within half an hour. A total of 8 units of blood and 6 g of fibrinogen had been administered.

Case 9

This patient was aged 25 years; para 1; gravida 5; and the gestational age was 37 weeks.

She was admitted as an emergency case, and presented with the classical signs and symptoms of a severe mixed variety of accidental haemorrhage. No fetal heart was detected. A coexistent coagulation disorder with fibrinolysis was diagnosed.

The cervix was found to be 4 cm dilated, fully effaced and the presenting part was cephalic. An artificial rupture of membranes was performed and whole blood given. Ten thousand units of heparin were administered intravenously and an oxytocin infusion was commenced. The patient delivered a 2 700 g fresh stillborn baby and more than 1 000 ml of retroplacental clot. There were no postpartum complications and the uterus remained well contracted. A total of 3 units of whole blood had been administered.

RESULTS

Table I illustrated the following features: uterine inertia was a feature in 7 of the 9 cases described. The administration

TABLE I. CLINICAL OUTCOME IN 9 CASES OF ACCIDENTAL HAEMORRHAGE WITH ASSOCIATED COAGULATION DISORDERS

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Trasylol given 4 hours before delivery	Yes	Yes	Yes	Yes	No	No	No	No	No
ARM and oxytocin infusion	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vaginal delivery	Yes	Yes	Yes	Yes	No	No	No	Yes (forceps delivery)	Yes
C/S for uterine inertia	No	No	No	No	Yes	Yes	Yes	No	No
Trasylol given immediately before C/S	—	—	—	—	No	Yes	Yes	—	—
PPH due to uterine atony	No	No	No	No	—	No	No	Yes	No
Severe haemorrhage at C/S	—	—	—	—	Yes	No	No	—	No
Maternal complications	No	No	No	Eclampsia and cerebral haemorrhage; died	No	Temporary renal shutdown	No	No	No
Fresh stillbirth	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

ARM = artificial rupture of membrane; C/S = Caesarean section.

of Trasylol was associated with a reawakening of uterine activity in all 4 cases where this drug was administered more than 4 hours before delivery.

In cases where Trasylol was not administered in order to re-establish uterine activity, the outcome was Caesarean section in 3 out of 5 cases. In the remaining 2 cases where spontaneous delivery occurred, labour was already established on admission.

Where Trasylol was administered before Caesarean section, bleeding due to uterine atony was not a feature.

Bleeding due to uterine atony occurred in 2 out of 3 cases where Trasylol was not administered at all (cases 5 and 8). In one case bleeding was in the form of postpartum haemorrhage after vaginal delivery. In the the other case it took the form of severe haemorrhage at Caesarean section.

DISCUSSION

Accidental haemorrhage rarely leads to severe maternal problems and most cases have an accelerated delivery. Some, paradoxically, appear to have depressed uterine activity.[2] In such cases, the fact that the fetus is usually dead, and that a coagulation disorder usually coexists, makes Caesarean section an undesirable and extremely dangerous alternative to vaginal delivery.

Basu[2] has shown that high levels of FDP (more than 1 024 μg/ml) inhibits uterine activity *in vitro*. Circulating levels of FDP do not reach this level, but uterine concentrations of FDP may well exceed this. Basu further suggests that where high levels of FDP exist, postpartum haemorrhage is a feature, and that the antepartum uterus does not appear to be affected to the same extent.[3]

This study suggests that high levels of FDP might inhibit uterine activity before delivery since uterine inertia was corrected after the administration of the fibrinolytic inhibitor, Trasylol. It has been suggested[4,5] that inhibition of myometrial activity might be due to kinins rather than FDP themselves. As increased fibrinolytic activity is associated with increased activity of the kallikrein system and thereby raised plasma levels of kinins, this possibility cannot be ruled out, but it is only of theoretical importance since Trasylol also inhibits kallikrein activity. The drug also limits the rate of intravascular coagulation by suppressing thromboplastin activity,[6] and thereby has an additional therapeutic effect.

The fibrinolytic system, besides being activated primarily after tissue injury, is also activated secondarily as a compensatory mechanism following disseminated intravascular coagulation. It is therefore likely that the administration of heparin may well potentiate the effect of Trasylol on uterine activity. At the same time heparin, largely by virtue of its antithrombin activity, effectively controls the consumption coagulopathy which is a feature of accidental haemorrhage with associated coagulation disorder.

Haemostasis at the uterine level is predominantly the result of occlusion of the vasculature which traverses the criss-cross muscle of this organ, rather than the effect of blood coagulation *per se*. It is, therefore, reasonable to assume that once uterine tone and contractability return, haemorrhage at the uterine level will slow down.

In conclusion, this study suggests a specific indication for the use of Trasylol in cases of severe accidental haemorrhage with coagulation defect where labour is not established. The likely mechanism is inhibition of fibrinolysis. Heparin, by inhibiting disseminated intravascular coagulation, will limit fibrinolysis as well and perhaps thereby potentiate the effect of Trasylol in such cases.

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