

Haemostatic effect of aprotinin during craniostomostic surgery in children

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Background: Aprotinin has been used in our hospital since the year 2003 to reduce bleeding during craniostomostic surgery in children. The aim of this retrospective study was to investigate its effect, primarily on bleeding and secondarily on the need for transfusion.

Methods: Thirteen children were treated with aprotinin from 2003 to 2008, while 39 were not treated in the period 1993–2002. Information on blood loss and need for transfusion during the operations in all 52 children was collected from their medical records.

Results: There was a significant difference in both blood loss and need for transfusion. Estimated blood volume was used to correct for difference in the children's age and size. In the

aprotinin group, blood loss was 3.9% of circulating blood volume vs. 22.0%, and the need for transfusion was 0.0% vs. 21.1%.

Conclusion: Blood loss and need for blood transfusion were significantly reduced in the aprotinin group. No allergic or other possible aprotinin-specific complications were registered in the aprotinin group.

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Introduction

CORRECTION of craniostomostosis is associated with significant amount of blood loss. In almost all cases, blood transfusion is needed. Transfusion of allogenic blood is not without complication, although the risk is low. Known risk factors are infections in the form of viral transmission and immunosuppression as well as transfusion-related lung injuries. To reduce blood loss and consequent risks, various methods and treatment strategies have been used such as cell salvage,^{1–3} transfusion of autogenic blood, recombinant erythropoietin to increase the red cell mass,^{1,4} and drugs effecting coagulation such as, e.g. tranexamic acid,^{4,5} aprotinin,⁶ and activated factor VII. Aprotinin has mainly been used to reduce blood loss in cardiac surgery. Its use in the paediatric population has also been mainly confined to cardiac surgery. However, aprotinin has also been tested with good results in other types of operations such as craniofacial surgery.⁶ Aprotinin is an allergenic protein, and an allergic reaction is therefore possible.⁷ The risk is increased on repeated exposures⁸ but seems to be reduced by

avoiding re-exposure within 6 months.⁷ Before using aprotinin, a test dose is recommended.^{6,7} Another risk linked to the use of aprotinin in heart surgery is increased occurrences of renal, cardiac, or cerebral events.⁹ The complications in this patient group most likely depend on the presence of atherosclerotic diseases which is not a problem in our population. So far, in paediatric surgery, there is no report of these complications.

The use of aprotinin has been restricted and it has even been withdrawn from the market due to complications in adult cardiac surgery. Only one published report has shown the benefit of using aprotinin to reduce bleeding and blood transfusion in the correction of craniostomostosis.⁶ Based on this report, we have, since 2003, used aprotinin routinely for this purpose in our hospital. Our feeling is that the use of aprotinin has dramatically changed our praxis both during operation and the post-operative period. The present retrospective study was done to investigate the effect of aprotinin on bleeding and need for transfusion during operation. From 2003 to 2008, 13 children were treated with aprotinin (aprotinin group). This group was compared to 39

children operated in the period 1993–2002 (control group). The primary end points were the amount of bleeding and given transfusion.

Methods

Medical records for children who underwent correction of craniosynostosis during both periods were reviewed. Demographic details, haemoglobin level, fluid, and transfusions requirements and complications during the operation were registered and analysed. Anaesthesia was usually induced and maintained by sevoflurane inhalation, except for the first 2 years when halothane was used. Neuromuscular relaxation and fentanyl were given as needed. After induction of anaesthesia, an intravenous line and arterial pressure line were inserted. Before surgery, the aprotinin group was given a 1.4-mg test dose of the drug. All the children in the aprotinin group were receiving the drug for the first time. If no sign of an allergic reaction was observed, the test dose was followed by a loading dose of 240 mg/m² over 20 min and, subsequently, an infusion of 56 mg/m² until the end of the surgery. Infusion of crystalloids and colloids (albumin) and transfusion of blood and blood components were based on clinical criteria and haematological parameters. To compensate for difference in age and body size, the blood loss and transfusion of blood was normalized by the use of estimated circulating blood volume of 80 ml/kg³. The study was approved by the Ethical Committee of the National University Hospital and the Data Protection Authority. Data analysis was performed using the SPSS software, Version 16.0 for Windows (SPSS Inc, Chicago, IL, USA). Normally distributed data are expressed as mean and standard deviation. Otherwise, the data are expressed as median and interquartile range. Mann–Whitney test was used to compare the difference between groups. The probability level of 0.05 was considered significant.

Results

Comparing the two periods, the children in the control group were somewhat older and larger than the children in the aprotinin group (Fig. 1 and Table 1).

The main finding of this study was a significant reduction in bleeding and transfusion for the aprotinin group (Table 2). Estimated blood loss was 3.9 [5.8]% of estimated blood volume (EBV) for the aprotinin group and 22.0 [16.6]% for the control group. The aprotinin group was transfused by 0.0

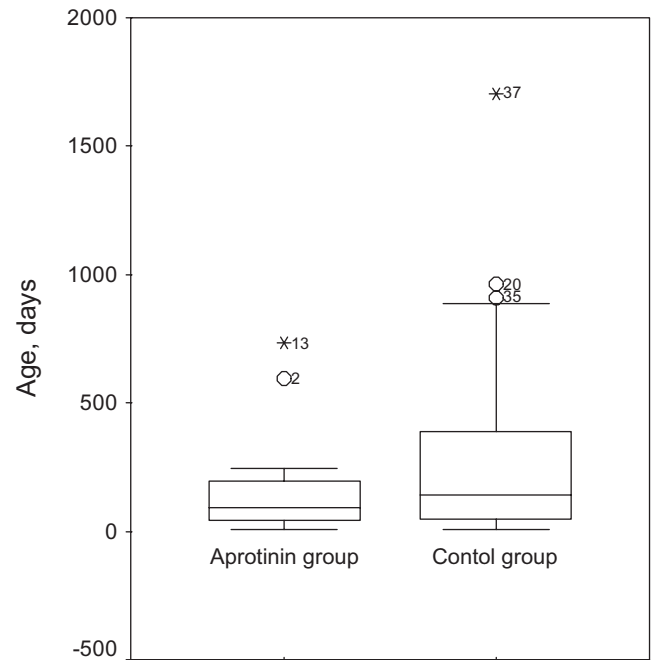


Fig. 1. Box plot graphic of age. Data are medians, 25th and 75th percentiles (box top and bottom) and non-outliers range (whiskers). The symbols ○ and * refer to outliers and extreme outliers.

Table 1

Demographic data of the aprotinin and control groups.

	Aprotinin group n = 13	Control group n = 39	P value
Age, days	89 [196]	143 [464]	0.86
Weight, kg	6.2 [3.7]	6.7 [6.6]	0.52
Length, cm	63.5 [14.3]	65 [21.8]	0.61
EBV	497.5 [312]	541 [621.5]	0.67

Values reported are median [interquartile range].
EBV, estimated blood volume.

Table 2

Blood loss, transfusion, and fluid given during the craniosynostotic correction in the aprotinin and control group are shown. All values are shown as percent of estimated blood volume.

	Aprotinin group n = 13	Control group n = 39	P value
Blood loss/EBV, %	3.9 [5.8]	22.0 [16.6]	<0.001
Transfusion/EBV, %	0.0 [0.0]	21.1 [22.0]	<0.001
Albumin/EBV, %	10.0 [6.9]	7.8 [17.7]	0.889
Crystalloid/EBV, %	18.6 [12.5]	21.8 [12.5]	0.267

Values reported are median [interquartile range].
EBV, estimated blood volume.

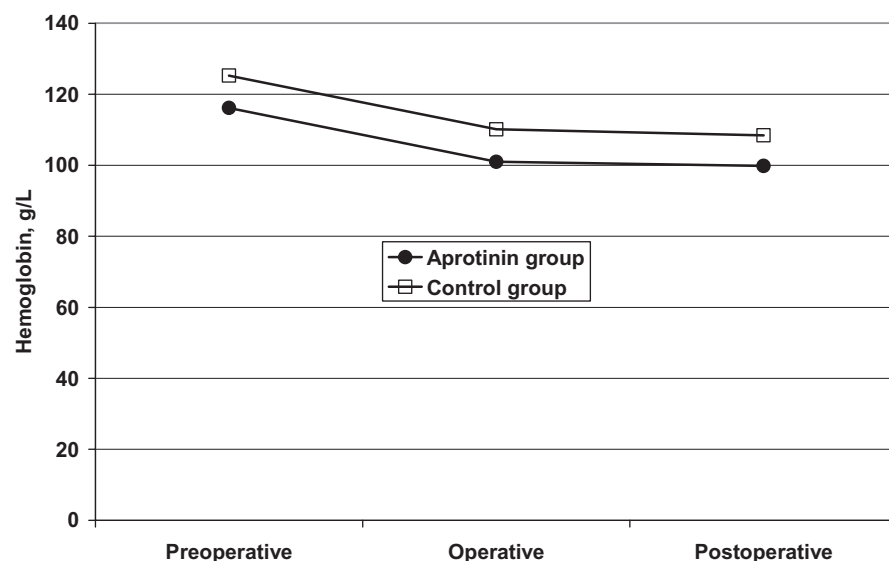


Fig. 2. The perioperative changes in haemoglobin concentration for both aprotinin and control groups are shown.

[0.0]% of EBV, whereas the control group was transfused by 21.1 [22.0]% of EBV. In the aprotinin group, only two children (15.4%) needed transfusion, one receiving 8.5% and the other receiving 15.4% of their EBV. In the control group, all the children got transfusion. Albumin and crystalloid fluids did not differ significantly between the groups (Table 2). The perioperative changes in haemoglobin concentration are shown in Fig. 2. The younger aprotinin group had a lower haemoglobin level from the start. The fall in haemoglobin during the operation was the same or about 16 g/l in both groups. No perioperative complication or allergic reaction was registered.

Discussion

This study has shown a fivefold reduction in bleeding in the aprotinin group compared with the control group. However, interpreting retrospective studies is always difficult because of possible multiple biases. All the operations were done by only two surgeons. During both periods, bone wax was used to locally control the bleeding from the bone edges. Before the introduction of aprotinin, bone wax was liberally used and usually covered the entire bone edges. Now, the use of bone wax is better focused to stop bleeding points. During the study periods, we were not aware of any changes in the operation technique that could explain this difference in bleeding. However, it is of course possible that during this 16-year period, increased operative skill could explain the reduction in bleeding. If so, a gradual decrease in bleeding would be expected over time. However, as can be seen in Fig. 3, there is a sudden

Table 3

Blood loss during craniostomy correction in control groups or operation without special intervention to reduce the need for allogenic transfusion.

	EBL/EBV, %	EBL/kg
Present study ($n = 39$)	26.1 ± 19.2	21.2 ± 15.1
Goobie et al. ⁵ ($n = 20$)		101 ± 63
Dadure et al. ⁴ ($n = 20$)		61.1 ± 16.8
D'Errico et al. ⁶ ($n = 60$)		39 ± 25
Fearon ² ($n = 21$)	28	19
Haas et al. ¹⁰ ($n = 9$)	80 [49–92]%	

Values reported are mean and standard deviation except the values from Haas et al. median and percentile.

EBL, estimated blood loss; EBV, estimated blood volume.

decrease in bleeding when the aprotinin treatment was introduced. As profuse bleeding usually begins immediately after starting the operation in the control group, transfusion was initiated almost straight away to maintain the circulation and oxygen transport. Soon after the aprotinin treatment started, we observed much slower bleeding and were thus able to use a much more conservative transfusion approach. This resulted in only two of the children being transfused during operation. Other studies have shown wide variation in operative bleeding. The magnitude of reported bleeding in published studies from the last decade during craniostomy correction has differed widely from 25% to 125% of EBV (Table 3). A multi-unit audit in the United Kingdom found that the need for transfusion in scaphocephaly correction was 100% of red cell volume.³ To lessen the risk of allogenic transfusion, three methods have principally been used: erythro-

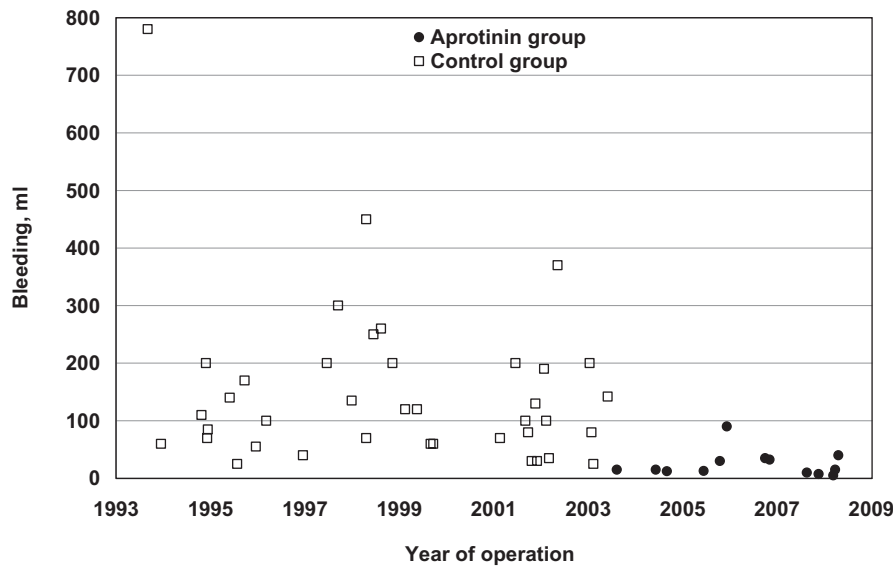


Fig. 3. The figure shows the estimated bleeding for each patient in both groups during the study period. There is an abrupt change in bleeding as aprotinin was introduced.

poietin to increase red blood cell mass, Cell Saver, and coagulating factors. Fearon,² using erythropoietin and Cell Saver, reported bleeding of 19 ml/kg (28.5% of EBV) and possible replacement of 15% of blood volume by cell saved blood, only 30% needing transfusion by allogenic blood. Krajewski et al.,¹ using the same method, found mean blood loss of 310 ml and transfused back 57.3 ml of Cell Saver blood. Only 5% needed transfusion with allogenic blood. They also found that of the 80% of the patients that at the end of the operation received cell saver blood, 31% would otherwise have needed allogenic blood. Dadure et al.⁴ also used preoperative erythropoietin in addition to tranexamic acid during operation. Although their study group's bleeding was 51.4 ml/kg, they only needed to transfuse 1.6 ml/kg intra-operatively. Only 11% in the study group needed transfusion compared with 45% in the control group. Goobie et al.⁵ also used tranexamic acid during operation. They found mean blood loss of 65 ml/kg and transfused 33 ml/kg of allogenic blood. D'Errico et al.⁶ studied the effect of aprotinin. They reported bleeding of 28 ml/kg in their study group and transfusion of 32 ml/kg of allogenic blood. Our results showing median blood loss of 3.9% of EBV and allogenic transfusion in only 15% of the patients are promising compared to others' use of more complex treatments. The main message from this retrospective study may be that by reducing the blood loss, the circulatory and often coagulation problem connected to heavy bleeding are much easier to master. After we started using aprotinin, the post-operative care has been changed

and moved from our intensive care unit to our usual post-operative ward.

Conclusion

Our findings indicate that the use of aprotinin during craniostynostotic surgery reduces bleeding. However, this is a retrospective study with many possible contradicting factors, and a more definite answer must wait for a prospective, randomized, and blinded study. The reduction in bleeding has made it possible for us to employ a more conservative transfusion approach.

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Conflicts of interest: Authors declare no conflicts of interest.

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