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Population pharmacokinetics of epsilon-aminocaproic acid in infants undergoing craniofacial reconstruction surgery

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Editor's key points

- This study aimed at determining the pharmacokinetics (PKs) of antifibrinolytic epsilon-aminocaproic acid (EACA) in infants aged 6–24 months undergoing craniofacial reconstruction surgery.
- The final structural model was a two-compartment disposition model with inter-individual random effects estimated on clearance and central distribution volume.
- EACA PKs is influenced by weight, age, and perioperative conditions.
- The dependence of clearance on body weight supports weight-based dosing.

Background. Understanding the clinical pharmacology of the antifibrinolytic epsilon-aminocaproic acid (EACA) is necessary for rational drug administration in children. The aim of this study is to determine the pharmacokinetics (PKs) of EACA in infants aged 6–24 months undergoing craniofacial reconstruction surgery.

Methods. Cohorts of six infants were enrolled sequentially to one of the three escalating loading dose–continuous i.v. infusion (CIVI) regimens: 25 mg kg⁻¹, 10 mg kg⁻¹ h⁻¹; 50 mg kg⁻¹, 20 mg kg⁻¹ h⁻¹; 100 mg kg⁻¹, 40 mg kg⁻¹ h⁻¹. Plasma EACA concentrations were determined using a validated high-performance liquid chromatography–tandem mass spectrometry assay. A population non-linear mixed effects modelling approach was used to characterize EACA PKs.

Results. Population PK parameters of EACA were estimated using a two-compartment disposition model with weight expressed as an allometric covariate and an age effect. The typical patient in this study had an age of 38.71 weeks and a weight of 8.82 kg. PK parameters for this typical patient were: pre-/postoperative plasma drug clearance of 32 ml min⁻¹ (3.6 ml kg⁻¹ min⁻¹), inter-compartmental clearance of 42.4 ml min⁻¹ (4.8 ml min⁻¹ kg⁻¹), central volume of distribution of 1.27 litre (0.14 litre kg⁻¹), and peripheral volume of distribution of 2.53 litre (0.29 litre kg⁻¹). Intra-operative clearance and central volume of distribution were 89% and 80% of the pre-/postoperative value, respectively.

Conclusions. EACA clearance increased with weight and age. The dependence of clearance on body weight supports weight-based dosing. Based on this study, a loading dose of 100 mg kg⁻¹ followed by a CIVI of 40 mg kg⁻¹ h⁻¹ is appropriate to maintain target plasma EACA concentrations in children aged 6–24 months undergoing these procedures.

Keywords: aminocaproic acid; antifibrinolytic agents; craniofacial abnormalities; infants; paediatrics; pharmacology

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Intraoperative haemorrhage during paediatric craniofacial reconstruction procedures often exceeds the circulating blood volume,^{1–3} mandating substantial perioperative transfusion.^{2,4,5} Transfusion of homologous blood products entails risks of infectious disease transmission, transfusion reaction, and immunosuppression.^{6–8} Efforts to minimize surgical bleeding may translate to reduced transfusion requirements and lessening of associated risks.

The intraoperative administration of antifibrinolytic agents is an increasingly used approach for minimizing blood loss and transfusion. The antifibrinolytic epsilon-aminocaproic acid (EACA) is a synthetic lysine analogue that blocks the lysine-binding sites on plasminogen, resulting in antifibrinolytic activity through inhibition of fibrinolysin formation.^{9,10} EACA has been shown to reduce transfusion requirements in children undergoing procedures on cardiopulmonary

bypass, as well as in adolescents undergoing spinal surgery for scoliosis.^{11–16} EACA may also be effective in reducing blood loss and transfusion in children undergoing craniofacial surgery; however, efficacy data to support the use for this indication are not yet available.

Before conducting efficacy studies, a firm understanding of the pharmacokinetics (PKs) of EACA in children is needed. Although EACA pharmacology has been well studied in adults,^{9 17–21} limited paediatric PK data are available to guide therapy or to guide dose selection for clinical trials.²² Given the need for PK data before conducting the clinical trials, the primary objective of this study was to describe the PKs of EACA administered to infants aged 2–24 months undergoing craniofacial surgery.

Methods

Clinical trial

This open-label, non-randomized, dose escalation, PK trial was conducted under an investigational new drug application (IND 105,301) with the United States Food and Drug Administration and registered at www.clinicaltrials.gov. After institutional review board approval and written informed parental consent, healthy infants aged 2–24 months undergoing craniofacial surgery without history of renal impairment or a history of a coagulation disorder were eligible for enrolment. Subjects were sequentially enrolled in one of the three cohorts. Each subject received an i.v. loading dose followed by a continuous i.v. infusion (CIVI) of EACA as described below:

	Loading dose (mg kg ⁻¹)	CIVI rate (mg kg ⁻¹ h ⁻¹)
Cohort 1	25	10
Cohort 2	50	20
Cohort 3	100	40

This dosage range was selected based on the dosing regimen reported in adolescents undergoing spinal fusion of 100 mg kg⁻¹ loading dose followed by a CIVI of 10 mg kg⁻¹ h⁻¹.¹⁵ EACA administration began in the operating theatre after induction of anaesthesia and arterial line insertion. The loading dose was administered over 10 min and was immediately followed by a CIVI that continued until the end of surgery as marked by completion of skin closure. Study enrolment continued until there were six evaluable subjects in each of the three cohorts. Interim PK and safety analyses were performed at the completion of each dosing cohort before escalation to the next higher dose cohort.

Patient characteristics and data pertaining to the medical management and perioperative course of enrolled subjects were collected. Collected data included age, weight, gender, diagnosis, surgical procedure, presence of a craniosynostosis syndrome, duration of surgery, and all fluids and blood products administered intraoperatively. Preoperative, intraoperative, and postoperative laboratory values performed as part of standard care were also recorded. The intensive care unit (ICU) flow sheets, progress notes, and

radiologic study results were reviewed to detect the occurrence of adverse events. Intraoperative blood loss was calculated in the manner previously described in this population by Kearney and colleagues²³ and used in other reports in this population.^{5 24}

Conduct of anesthesia

All subjects received general tracheal anaesthesia with standard American Society of Anesthesiologists monitoring. Mask induction of anaesthesia was performed with sevoflurane, nitrous oxide, and oxygen. Each subject had two peripheral i.v. catheters: a central venous catheter and a radial arterial catheter placed as part of our standard clinical care. Normothermia was facilitated by a circulating warm water blanket, a forced air warmer, and an i.v. fluid warmer. Anaesthesia was maintained with isoflurane, sevoflurane, or desflurane in air and oxygen. Fentanyl or morphine was administered for anaesthetic supplementation and postoperative analgesia. Anaesthetic management, fluid management, and blood loss replacement were at the discretion of anaesthesia providers without a fixed protocol. Standard clinical practice at our institution is to direct fluid and anaesthetic management to maintain a mean arterial pressure >45 mm Hg in these children.

PK sampling

PK samples, consisting of 1 ml of blood, were drawn immediately before and after the loading dose, after initiation of CIVI (0.5, 2, 4–6 h), at the end of the CIVI, and after the end of the CIVI (0.5, 3, 6, 9, 12, and 15 h), for a maximum total of 12 PK samples. All intraoperative PK samples were drawn from the arterial catheter. Postoperative PK samples were drawn from an arterial catheter or central venous catheter; nearly all were arterial. Plasma was separated by centrifugation and stored at –80°C.

Drug quantitation

EACA plasma concentrations were determined using a validated high-performance liquid chromatography-tandem mass spectrometry assay with a lower limit of quantitation of 1 µg ml⁻¹. The intraday precision based on the standard deviation of replicates of quality control samples ranged from 0.3% to 2% with accuracy ranging from 89% to 102%. The method was validated for EACA concentrations of 1–250 mg litre⁻¹.

Pharmacostatistical analysis

Model building

The population PK analysis was conducted using non-linear-mixed effects methods (NONMEM[®] software, ICON Development Solutions, Ellicott City, MD, USA, version VI, level 2.0 with subroutines ADVAN 3, TRANS 4). All models were run with the first-order conditional estimation with interaction (FOCE-I) method. S-Plus Version 6.2 (Insightful, Inc., Data Analysis Products Division, Seattle, WA, USA) was used for goodness-of-fit diagnostics and graphical

displays. The goodness-of-fit from each model run was assessed by the examination of the following criteria: diagnostic plots, the standard errors of the parameters, global minimization of the search algorithm, the Akaike Information Criterion which is equal to the minimum objective function value (MOFV) plus two times the number of parameters, and plausibility of parameter estimates.

Base model

One, two, and three-compartment models were investigated. A two-compartment disposition model was selected to define the EACA plasma concentration profile based on results from the model building process and previously published data.^{9 17} Models were parameterized by clearance (CL, ml min⁻¹), inter-compartmental clearance (Q, ml min⁻¹), central volume of distribution (V1, litres), and peripheral volume of distribution (V2, litres). The one-compartment model was inadequate to describe the data. The added complexity of the three-compartment model was not supported by the data.

An exponential variance model was used to describe the variability of PK parameters across individuals in the form: $P_i = \theta_k \exp(\eta_{ki})$, where P_i is the estimated parameter value for the individual subject i , θ_k is the typical population value of parameter k , η_{ki} are the inter-individual random effects for individual i and parameter k . Inter-individual variability was initially estimated for clearance, and then subsequently for the remaining PK parameters.

Additive, proportional, and combined (additive and proportional) residual error models were considered during the model-building process. Ultimately, a combined additive and proportional error model was used to describe random residual variability: $C_{obs,ij} = [C_{pred,ij} \times (1 + \varepsilon_{ijp})] + \varepsilon_{ijA}$, where $C_{obs,ij}$ is the observed concentration j in individual i , $C_{pred,ij}$ is the individual predicted concentration, ε_{ijp} is the proportional residual random error, and ε_{ijA} is the additive residual random error for individual i and measurement j .

The impact of weight on all parameters was implemented using an allometric model: $TVP = \theta_{TVP} \times (WT_i / WT_{ref})^{\theta_{allometric}}$, where TVP is the typical value of a model parameter, described as a function of body weight, θ_{TVP} is an estimated parameter describing the typical PK parameter value for an individual with weight equal to the reference weight, WT_i is an individual subject's body weight and WT_{ref} is the reference value (8.82 kg for this analysis), and $\theta_{allometric}$ is an allometric power parameter based on physiologic consideration of size impact on metabolic processes and is fixed at a value of 0.75 for clearances, and a value of 1 for volumes.²⁵

Full covariate model

A full covariate model was constructed to make inferences about effects of covariates on EACA disposition. Covariate effects were pre-defined based on clinical interest, prior knowledge, and physiologic plausibility. The analysis was focused on estimation of effects and avoided the problem

of selection bias, which is particularly problematic with step-wise model building in small data sets.^{26 27} The effects of age, intra- vs postoperative status, and blood loss were evaluated in this model.

Simulations

The full covariate model was used to simulate expected concentration–time profiles under various dosing scenarios. Five hundred Monte Carlo simulation replicates were performed to determine the optimal dose to achieve plasma steady-state concentrations >130 mg litre⁻¹, which have been associated with therapeutic EACA effects.^{28 29} A bolus dose over 10 min followed by a 240 min infusion was simulated for the median subject (8.82 kg child, 38 weeks of age), the youngest subject in the cohort (7.7 kg, 27 weeks) and the oldest child in the cohort (11.8 kg, 107 weeks), who all had an operative procedure of 240 min. The median concentration and the 95% confidence interval were estimated.

Safety monitoring

All subjects who received at least the loading dose of EACA were part of the safety population. All enrolled subjects had the following preoperative laboratory tests: complete blood count, prothrombin time (PT), activated partial thromboplastin time (aPTT), blood urea nitrogen (BUN), and serum creatinine. Subjects who consented but who had preoperative laboratory evidence of abnormal renal function, coagulation derangement, or haematologic abnormality on screening laboratory testing were considered screen failures and were not eligible to receive study drug.

A dose-limiting toxicity (DLT) was defined as a decrease in mean arterial blood pressure of >30% of the baseline value during EACA loading dose administration or any serious adverse event possibly, probably, or definitely related to EACA administration. In the event that two of the six subjects in a dosing cohort experienced a DLT, three additional subjects to a maximum of nine would have been enrolled in that dosing cohort. The maximum tolerated dose for EACA would have been exceeded if one additional subject demonstrated a DLT, and no additional subjects would be studied in that dosing cohort. All subjects had the following testing on postoperative day 1 for safety evaluation: BUN, creatinine, PT, aPTT, serum aspartate aminotransferase, serum alanine transaminase (ALT), and total bilirubin level. After completion of enrolment of each cohort and before dose escalation to the next cohort, EACA assays were performed and adverse events were reviewed with the study medical monitor (a physician not involved in the conduct of the study).

Results

Study conduct

One hundred and eighty-two potentially eligible subjects were screened for enrolment. Of these, 43 subjects met the initial eligibility criteria and 39 subjects were approached for enrolment. Of these, 18 subjects were enrolled in the

Table 1 Subject patient characteristics

	ID	Weight (kg)	Age (weeks)	Gender	Diagnosis	Procedure
Cohort 1	1	7.7	27.4	Female	Unicoronal synostosis	Fronto-orbital advancement
	2	9.6	38.9	Male	Metopic synostosis	Fronto-orbital advancement
	3	7.9	31.6	Male	Lambdoid synostosis	Posterior cranial vault reconstruction
	4	11.4	85.9	Female	Pfeiffer syndrome	Fronto-orbital advancement
	5	8.3	38.6	Female	Unicoronal synostosis	Fronto-orbital advancement
	6	7.8	34.6	Female	Saethre-Chotzen syndrome	Fronto-orbital advancement
Cohort 2	7	10.8	67.1	Male	Sagittal synostosis	Fronto-orbital advancement
	8	6.7	69.4	Female	Metopic synostosis	Fronto-orbital advancement
	9	8.9	99	Female	Metopic synostosis	Fronto-orbital advancement
	10	6.8	33	Male	Unicoronal synostosis	Fronto-orbital advancement
	11	9.9	34.9	Male	Metopic synostosis	Fronto-orbital advancement
	12	7.4	30.6	Female	Metopic synostosis	Fronto-orbital advancement
Cohort 3	13	8.7	35	Female	Metopic synostosis	Fronto-orbital advancement
	14	11.8	106.9	Female	Sagittal synostosis	Posterior cranial vault reconstruction
	15	9.1	42.1	Female	Metopic synostosis	Fronto-orbital advancement
	16	10.9	48.7	Male	Metopic synostosis	Fronto-orbital advancement
	17	7.1	36.4	Male	Metopic synostosis	Fronto-orbital advancement
	18	10.2	43.7	Male	Unicoronal synostosis	Fronto-orbital advancement

Table 2 Intraoperative calculated blood loss and i.v. fluid and transfusion volumes

Subject #	Weight (kg)	Calculated blood loss (blood volumes)	Calculated blood loss (ml)	Lactated Ringer's (ml)	Reconstituted blood (ml)
1	7.7	0.2	118	300	110
2	9.6	1.0	920	200	750
3	7.9	0.5	345	200	225
4	11.4	1.1	1170	350	975
5	8.3	1.2	1001	550	840
6	7.8	0.9	571	500	500
7	10.8	1.7	1676	825	1300
8	6.7	0.4	242	300	170
9	8.9	1.0	822	700	600
10	6.8	1.0	580	455	405
11	9.9	1.4	1334	350	935
12	7.4	2.0	1284	425	1030
13	8.7	1.1	930	350	600
14	11.8	1.2	1317	350	1083
15	9.1	1.0	907	600	760
16	10.9	0.4	412	300	220
17	7.1	1.7	1079	250	910
18	10.2	0.9	821	450	630

study, all of whom were subsequently included in the PK analysis. Patient characteristics of evaluable subjects are presented in Table 1. The median age and weight of the subjects were 39 weeks and 8.8 kg, respectively. Intraoperative fluid administration and calculated blood loss are presented in Table 2. The median (range) duration of the CIVI was 230 (111–342), 227 (169–365), and 254 (219–280) min in cohorts 1, 2, and 3, respectively, with an overall median duration of infusion of 243 min.

PK modelling and simulation

Concentration–time profiles are presented in Figure 1. The final structural model was a two-compartment disposition model with inter-individual random effects estimated on CL and V1. The addition of inter-individual variability estimates on Q and V2 resulted in over-parameterization of the model, as evidenced by failure of the covariance step, and these terms were not included in the final model. Using FOCE-I estimation, the base model minimized with

Fig 1 Semi-logarithmic concentration–time plots for aminocaproic acid for the three dosing cohorts. Pre-bolus concentrations are omitted (all less than the lower limit of quantitation). Plasma concentrations obtained before and after end of infusion (time 0) are shown. End of infusion occurs at 0 h. (A) Dosing cohort 1: intravenous loading dose administered over 10 min of 25 mg kg⁻¹ followed by a CIVI of 10 mg kg⁻¹ h⁻¹. (B) Dosing cohort 2: loading dose of 50 mg kg⁻¹ followed by a CIVI of 20 mg kg⁻¹ h⁻¹. (C) Dosing cohort 3: loading dose of 100 mg kg⁻¹ followed by a CIVI of 40 mg kg⁻¹ h⁻¹.

Fig 1 Continued

successful execution of the covariance matrix of the estimates. Scaling the PK parameters allometrically to weight resulted in a 29-point improvement in the minimal value of the objective function when compared with a model without weight. The full covariate model was developed by simultaneously including effects for covariates of clinical interest and those with physiological plausibility. Table 3 demonstrates key modelling steps in the development of the full PK model.

The impact of intra-operative blood loss on PKs was of clinical interest. Given the study design, however, this covariate was temporally correlated with the intra-operative period, and any associated physiological or pharmacological changes during that time. Consequently, a definitive estimation of intra-operative blood loss effects was not possible. The difference between intra- and pre-/postoperative CL and V1 was estimated in the modelling effort, and this effect is understood to include the impact of blood loss and other changes during the intra-operative period. The intra-operative period (the time when bleeding occurred) was defined as the time immediately after the post-loading dose PK sample through the end of the surgery. The differences in CL and V1 were estimated for this period relative to the pre-/postoperative period. There was an 11% (SE

7.9%) reduction in CL during the intra-operative period, and a 20% reduction in V1 (SE 16.6%).

Review of the exploratory graphics of the random effects for CL demonstrated that a strong correlation between age and CL (Fig. 2A) remained after the addition of weight as a covariate. The addition of age as a covariate on CL resulted in an improvement in the random effects for CL vs age (Fig. 2B). The model for the age-related maturational effect on CL was implemented as an asymptotically increasing maximum effect model. The model-estimated age at which 50% of full CL was achieved was 7.36 (55.4% SE) weeks. The precision of this parameter reflects the fact that the observed age range lower bound was 24 weeks. Given this point estimate, however, it is expected that 90% of full maturation CL should occur at ~66 weeks.

Observed vs population and individual predicted values revealed no systematic bias in the prediction of plasma concentrations for the entire study (Fig. 3). Final parameter estimates, inter-individual variability, and residual variability are represented in Table 4, with the respective standard errors of the point estimates. Table 5 reports CL and V1 for various weight groups without an age effect. We estimate the typical values of pre-/postoperative CL for a 70 kg adult to be 177.7 ml min⁻¹ 70 kg.

Table 3 Key modelling steps in the development of the full PK model. BSV, between-subject variability; MOFV, minimum objective function value

Run	Original run	Comments	MOFV	Change in MOFV	Execution of covariance step	Comments
1		No weight, BSV on CL and V1	872		Yes	
2	1	Weight added	843	−29	Yes	
3	2	Add BSV to Q	831	−12	No	Improvement in MOFV but failure of covariance step
4	2	Add BSV to V2	837	−6	No	Improvement in MOFV but failure of covariance step
6	2	Age added	841	−2	Yes	Improvement in random effects
10	5	Difference in CL and V1 pre/postoperative vs intraoperative	836	−5	Yes	Final model

Fig 2 Random effects (η) for CL vs age from the weight model (A) and final (B) models.

Dosing scenarios were explored by simulation with the final model. These simulations predicted that a loading dose of 100 mg kg^{-1} followed by a continuous infusion of $40 \text{ mg kg}^{-1} \text{ h}^{-1}$ for 4 h would be expected to maintain a steady-state plasma concentration of $\sim 130 \text{ mg litre}^{-1}$ in $\sim 95\%$ of subjects for the duration of the infusion for the median subject (8.82 kg child, 38 weeks of age). Similar concentrations were achieved for the youngest subject in the cohort (7.7 kg, 27 weeks) and the oldest child in the cohort (11.8 kg, 107 weeks) with the same dosing strategy (Fig. 4).

Safety evaluation

No subject in this study experienced a DLT. No adverse events were identified to be possibly, probably, or definitely related to EACA administration.

Discussion

A typical infant in this study (median weight of 8.82 kg, 38.7 weeks) undergoing craniofacial reconstruction surgery had a

pre-/postoperative plasma drug clearance of 32 ml min^{-1} ($3.6 \text{ ml kg}^{-1} \text{ min}^{-1}$), inter-compartmental clearance of 42.4 ml min^{-1} ($4.8 \text{ ml min}^{-1} \text{ kg}^{-1}$), central volume of distribution of 1.27 litre ($0.14 \text{ litre kg}^{-1}$), and peripheral volume of distribution of 2.53 litre ($0.29 \text{ litre kg}^{-1}$) based on a two-compartment population PK model. Intra-operative clearance and central volume of distribution were 89% and 80% of the pre-/postoperative value, respectively. Age effect on CL remained after accounting for weight, and was poorly estimated as demonstrated by the per cent standard error. Maturation of CL was described with a half-maximal capacity by ~ 7.3 weeks, and full maturation by 66 weeks. Because all intraoperative blood loss occurred more than 10 min after the completion of the loading dose, values for V1 derived from the intra-operative period should not be used when determining the loading dose. The intra-operative V1 was less than that of the pre- and postoperative settings. The use of the intra-operative value therefore would result in an underestimation of the required loading dose.

Previous studies have shown that renal excretion serves as the primary route of EACA elimination, whether administered

Fig 3 Observed vs population (A) and individual (B) predicted concentrations for the full model. A loess smoother is represented by the dashed line.

orally or i.v.^{9 30–32} Approximately 65–75% of the dose is recovered in the urine as unchanged drug while ~11% of the dose appears as the metabolite adipic acid.^{9 17 30–32} Based on our data, we estimate a typical postoperative clearance of $184.4 \text{ ml min}^{-1}$ for a 70 kg person, which compares favourably to the previously reported clearance of 190 ml min^{-1} for a 70 kg adult ($157 \text{ ml h}^{-1} \text{ kg}^{-1}$) reported by Frederiksen and colleagues⁹ and the clearance of 124 ml min^{-1} ($106 \text{ ml h}^{-1} \text{ kg}^{-1}$) reported by Dvorchik and colleagues.³³ We hypothesize that EACA has a high extraction ratio and that intra-operative clearance is less than postoperative clearance possibly because of anaesthetic-related decreases

in blood pressure, cardiac output or both, resulting in less renal perfusion and, therefore, a decrease in the perfusion-limited CL.

The therapeutic plasma concentration of EACA to control systemic fibrinolytic activity was determined to be $130 \text{ mg litre}^{-1}$ ($1 \text{ mmol litre}^{-1}$) in 1959.^{28 29} Dosing strategies based on PK studies in adults^{18 19} and children²² have been targeted to maintain plasma EACA levels at or above this concentration. Based on our data, an EACA loading dose of 100 mg kg^{-1} administered over 10 min followed by a CIVI of $40 \text{ mg kg}^{-1} \text{ h}^{-1}$ would yield therapeutic plasma EACA concentrations for the typical subject (38 weeks, 8.82 kg). The PK

model described provides our best understanding of drug disposition. The model was used to evaluate a simpler dosing rule that is commonly used as a standard of care. This dosing strategy was not model derived. A simpler dosing rule for clinical use was proposed, and this was evaluated using the rigorous model. The dosing rule that is used in clinical practice achieved target concentrations when evaluated by the PK model, and therefore more complex dosing rules are not indicated for use at the bedside. Frederiksen and colleagues reported that the peak antifibrinolytic effects of EACA occurred 15–60 min after peak plasma concentrations were achieved.⁹ Accordingly, the completion of the loading dose should occur at least 15 min before surgery begins.

Table 4 Parameter estimates from the full covariate EACA population pharmacokinetic model. SE%=(standard error/parameter estimate) × 100. Between-subject variability=(square-root of variance) × 100. Covariance between CL and V1 random effects was 0.03 (102% SE). Postoperative CL = $\theta_{CL} \times (WT/8.82)^{0.75} \times (age)/(7.36 + age)$. Intra-operative CL = post-/postoperative CL × 0.89. V1 = $\theta_{V1} \times (WT/8.82)^1$. Intra-operative V1 = post-/postoperative V1 × 0.8. Q = $\theta_Q \times (WT/8.82)^{0.75}$. V2 = $\theta_{V2} \times (WT/8.82)^1$

Parameter	Estimate	SE%
Postoperative CL (ml min ⁻¹)	37.6	7.9
Ratio of intra-operative CL to postoperative CL	0.89	4.3
V1 (litre)	1.27	13.6
Ratio of intra-operative V1 to postoperative V1	0.8	16.6
Q (ml min ⁻¹)	42.3	5.2
V2 (litre)	2.53	55.4
Age of 50% CL (weeks)	7.36	16.6
Parameter	Between-subject variability	SE%
ω^2_{CL}	16.79	33.9
ω^2_{V1}	47.01	72.4
Residual variability	Variance	SE%
$S^2_{proportional}$	0.03	27.9
$S^2_{additive}$	0.6	22.6

Blood loss is a significant concern in children undergoing cranial vault reconstruction surgery. Large scalp dissections and the performance of large craniotomies and osteotomies, together with the potential for dural venous sinus bleeds, provide opportunities for significant intraoperative haemorrhage. Multiple strategies have been devised for reducing blood loss and transfusion in this population, including pre-operative erythropoietin administration,^{34–37} reinfusion of shed blood,² acute preoperative normovolemic haemodilution,^{34, 38} use of fibrinogen concentrates,³⁹ prophylactic administration of fresh frozen plasma,^{24, 40} and administration of antifibrinolytic drugs.^{5, 41, 42} Of these, the use of antifibrinolytics has notable advantages. These drugs are simple to administer, are well tolerated, require no additional office visits or surveillance lab testing (when compared with erythropoietin), and require no additional equipment beyond an infusion pump (in contrast to cell saver or acute preoperative normovolemic haemodilution). Furthermore, there is a growing body of evidence supporting the efficacy of antifibrinolytics in infants and children undergoing craniofacial surgery, as two recent randomized, blinded clinical trials have shown the antifibrinolytic tranexamic acid (TXA), another synthetic lysine analogue, to be effective in reducing blood loss and transfusion requirements in this population.^{5, 42}

These recent clinical trials justify conduct of a prospective clinical trial of EACA to determine whether it is also effective in reducing blood loss. The PK data from this study will enable the use of a dosing strategy designed to achieve therapeutic drug concentrations, an essential element for the conduct of a valid efficacy study with EACA. If similarly efficacious, EACA would be a useful and less-expensive alternative to TXA (US \$597 for ten 100 mg ml⁻¹ 10 ml single-dose vials of TXA vs US \$123 for ten 100 mg ml⁻¹ 10 ml single-dose vials of EACA, personal communication with our hospital pharmacy). Having two efficacious antifibrinolytics would also be useful given the potential for interruptions in the availability of injectable medications.^{43–45}

Unlike typical PK studies in volunteers, the subjects in this study underwent surgical procedures with significant blood loss. We hypothesized that a study drug was eliminated not only by renal and metabolic processes, but also through direct loss via haemorrhage. Modelling results, however, revealed that intraoperative CL was found to be

Table 5 Pre-/postoperative and intraoperative CL and V1 estimates for various weights without age adjustment

Weight (kg)	Pre-/post-op. CL (ml min ⁻¹)	Pre-/post-op. CL (ml kg ⁻¹ min ⁻¹)	Intra-op. CL (ml min ⁻¹)	Intra-op. CL (ml kg ⁻¹ min ⁻¹)	Pre-/post-op. V1 (litre)	Pre-/post-op. V1 (litre kg ⁻¹)	Intra-op. V1 (litre)	Intra-op. V1 (litre kg ⁻¹)
1	7.35	7.35	6.54	6.54	0.14	0.14	0.12	0.12
5	24.56	4.91	4.37	0.87	0.72	0.14	0.58	0.12
10	41.31	4.13	3.68	0.37	1.44	0.14	1.15	0.12
15	56.00	3.73	3.32	0.22	2.16	0.14	1.73	0.12
25	82.14	3.29	2.92	0.12	3.60	0.14	2.88	0.12
50	138.14	2.76	2.46	0.05	7.20	0.14	5.76	0.12
70	177.79	2.54	2.26	0.03	10.08	0.14	8.06	0.12

Fig 4 Simulated plasma EACA concentrations ($\mu\text{g ml}^{-1}$) after a 100 mg kg^{-1} bolus over 10 min followed by a $40 \text{ mg kg}^{-1} \text{ h}^{-1}$ infusion for 4 h (240 min) in a 8.82 kg, 38-week-old child (a), the youngest subject in the cohort (7.7 kg, 27 weeks; b) and the oldest subject in the cohort (11.8 kg, 107 weeks; c), who all experienced an operative procedure of 240 min. The solid line represents the median concentrations. The dashed lines represent the 2.5th (lower) and 97.5th (upper) percentiles.

less than postoperative CL. This finding is not completely inconsistent with bleeding as an elimination mechanism, in that the model results may be simply reflecting the net effect of a possible increased CL due to blood loss and decreased CL due to other confounding intra-operative factors. The magnitude of the intra-operative decrease in CL corresponds to an expected increase in steady-state concentrations of ~15% during this period, relative to the post-operative period.

Limitations

Although sample size was a potential limitation of this study, the structural PK parameters were precisely estimated. Previous PK studies of EACA in adults have included 6 subjects,⁹ 10 subjects,³³ and 16 subjects.³¹ The only available PK study in children involved nine subjects who underwent procedures on cardiopulmonary bypass.²² There are many conditions in the operating theatre that may impact clearance and volume of distribution, such as blood loss, fluid administration, anaesthetic-induced decreases in blood pressure and cardiac output that may result in decreased organ blood flow. As described earlier in the Methods section, this makes unique estimation of any one of these effects on parameter estimates unidentifiable; therefore we used the intra-operative period as a categorical variable to estimate the changes in CL.

We did not perform thromboelastography to assess the effects of EACA in this study. The therapeutic goal of intra-operative EACA administration is to achieve plasma levels that completely inhibit fibrinolysis. This plasma concentration was determined to be 130 $\mu\text{g ml}^{-1}$ by *in vitro* testing of adult plasma by McNicol and colleagues.³¹ These findings were recently independently confirmed.⁴⁶ Interestingly, Goobie and colleagues⁵ showed no differences in thromboelastographic measurements between placebo and TXA groups despite therapeutic plasma TXA concentrations and a 40% reduction in transfusion. Based on the above, thromboelastography was unlikely to have been a useful measurement in the present study. It should also be noted that we have assumed that the therapeutic EACA plasma concentration in adults is also therapeutic in infants and children, whose coagulation and fibrinolytic systems are still developing.^{47–48} The available evidence shows that significantly lower plasma concentrations of EACA are required to completely prevent fibrinolysis in neonatal plasma.⁴⁶

Conclusions

Epsilon-aminocaproic acid PKs is influenced by weight, age, and perioperative conditions. Weight-based dosing in this population is appropriate, and based on the modelling from this study, a loading dose of 100 mg kg^{-1} followed by a CIVI of 40 $\text{mg kg}^{-1} \text{h}^{-1}$ is appropriate to maintain target plasma EACA concentrations in patients 6–24 months of age undergoing these procedures. EACA was well tolerated and no adverse events were attributed to its administration. A prospective efficacy trial using the dosing

recommendations from this study evaluating the efficacy of EACA in this population is suggested.

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Declaration of interest

None declared.

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Authors' contributions

P.A.S.: study design, conduct of study, data collection, data analysis, manuscript preparation; A.F.Z.: study design, conduct of study, data analysis, manuscript preparation; J.E.F.: study design, conduct of study, manuscript preparation; L.G.M.: conduct of study, manuscript preparation; E.M.S., E.Y.P., and T.K.G.: conduct of study, data collection; M.R.G.: data analysis, manuscript preparation; J.A.T. and S.P.B.: conduct of study; M.S.S.: study design, manuscript preparation.

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