

Accepted Manuscript

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PII: S1010-5182(16)30116-0

DOI: 10.1016/j.jcms.2016.06.028

Reference: YJCMS 2411

To appear in: *Journal of Cranio-Maxillo-Facial Surgery*

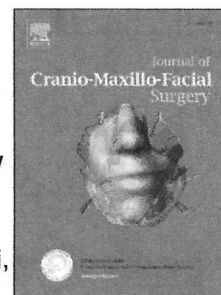
Received Date: 12 February 2016

Revised Date: 22 May 2016

Accepted Date: 27 June 2016

Please cite this article as: Stehrer R, Hunger S, Schotten K-J, Parsaei B, Malek M, Jacob M, Geiselseder G, Meier J, Reduction of transfusion requirements in pediatric craniosynostosis surgery by a new local hemostatic agent, *Journal of Cranio-Maxillofacial Surgery* (2016), doi: 10.1016/j.jcms.2016.06.028.

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Reduction of transfusion requirements in pediatric craniosynostosis surgery by a new local hemostatic agent

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No funding or support in the form of grants was obtained or used for this study.

INTRODUCTION

Premature bony fusion of cranial sutures results in the clinical syndrome of craniosynostosis (Zöller and Mühling, 2012). As described initially by Virchow, the ossified suture inhibits skull growth perpendicular to the affected suture leading to compensatory expansion towards the affected suture (Virchow, 1851/1852). The frequency of craniosynostosis has been estimated 3 to 5 individuals per 10 000 live births (Kimonis *et al.*, 2007).

The most important cornerstone of effective therapy is early, individualized surgical treatment with the aim to avoid serious complications such as cerebral atrophy associated with functional disorders and mental retardation as a result of high intracranial pressure (Renier *et al.*, 2000).

However, surgical therapy of craniosynostosis is associated with severe perioperative bleeding due to venae emissariae of the cranium that are exposed after subgaleal and pericranial flaps are detached. Since corrective surgery is mainly performed in infants with low circulating blood volume, large amounts of packed red blood cell (PRBC) and human plasma transfusions (Octaplas SD, Octapharma GmbH, Vienna, Austria) are needed to avoid dangerous degrees of anemia in these patients (van Uitert *et al.*, 2011, Pietrini, 2013).

In order to avoid unnecessary transfusions, blood loss from venae emissariae is regularly reduced by the usage of bone wax (Knochenwachs, B. Braun Surgical, S.A., Rubi, Spain), which occludes larger vessels effectively, but fails to reduce diffuse and continuous blood loss from the many small venae emissariae. As a consequence, diffuse bleeding from small vessels remains one of the most important determinants of the amount of blood loss during craniosynostosis surgery.

In 2008 SeraSeal® (Haemo-Pharma Consult GmbH, Hornstein, Austria) was introduced as a potential supplement to bone wax in craniosynostosis surgery in Austria. SeraSeal® is a CE-

certified topical hemostatic agent which consists of the complex sugar Agar and the coagulation factors II, VII, IX and X, derived from bovine plasma (*Xerasal*). It catalyzes and supports blood clotting, and also works in anticoagulated patients or patients with coagulation factor deficiency. Its mode of action might help to reduce diffuse bleeding from small venae emissariae during craniostomy (*Xerasal*). However, efficacy of SeraSeal® to reduce perioperative bleeding in the setting of craniostomy in children has not been demonstrated yet.

Therefore it is the aim of this study to evaluate whether the combination of SeraSeal® and bone wax results in a significant reduction of perioperative transfusion requirements in contrast to standard treatment with bone wax alone in children undergoing craniostomy surgery.

MATERIAL AND METHODS

Study design

The trial was designed as an observational study with a retrospective control group (23 children) and a prospective verum group (12 children). Children in the retrospective control group underwent surgery for craniostomy repair between April 2009 and September 2012. The consecutive enrollment period for the prospective SeraSeal® group was from September 2012 to January 2014. We excluded children younger than 6 months or older than 2.5 years, children suffering from syndromic craniostomy, children with bleeding diathesis, clotting abnormalities or children with vascular malformation in the cephal region, since these comorbidities are known to increase perioperative blood loss (*White et al., 2009*). We also excluded patients with bovine protein allergy as affected patients could overreact to SeraSeal®. Furthermore patients with hereditary anemias and proliferative diseases of bone marrow were

excluded. The trial was approved by the Ethics Committee of Upper Austria (K-40-13) and the Ethics Committee of the faculty of Medicine of the Ludwigs-Maximilians-University Munich (1-14). Informed parental consent was obtained for children in the SeraSeal® group.

Surgical and anesthesia procedure

All surgical procedures were performed by the same team of surgeons (cranio-maxillofacial surgeon M.M. and neurosurgeon B.P.). All of the anesthesiologists were experienced consultants. The operations took place at the State Women's and Children's Hospital Linz, Austria, whereas the perioperative medical and outpatient care was realized by the department of Cranio-Maxillofacial Surgery of the General Hospital of the city Linz (AKH), Austria, under the supervision of the surgeon M.M.

All children underwent standard monitoring according to the individual decision of the attending anesthesiologist. Antibiotic prophylaxis and local anesthesia was performed similarly in both groups according to standard operating procedures established at our institution.

In both groups general anesthesia was induced by inhalative sevoflurane (SEVOrane, AbbVie GmbH, Vienna, Austria) and intravenous sufentanil (Sufenta, Janssen-Cilag Pharma GmbH, Vienna, Austria) according to the assessment of the attending anesthesiologist. Patients were tracheally intubated and ventilated mechanically. Tidal volume and respiration rate was set to maintain normocapnia. Anaesthesia was maintained by a continuous application of sevoflurane and continuous infusion of remifentanil (Ultiva, GlaxoSmithKline Pharma GmbH, Vienna, Austria) according to the anesthesiologist. In both groups insensible fluid losses were substituted

by continuous infusion of crystalloids (ELO-PAED balanced 1% glucose and ELO-MEL isoton, both Fresenius Kabi GmbH, Graz, Austria) with an infusion rate of 5 ml/kg per hour. In both groups mean arterial blood pressure was intended to keep within the limits of 45 to 65 mmHg.

After the induction of general anesthesia, surgery was performed in both groups by a bi-coronal wavelike incision. All children in both groups were operated using solely open cranial vault remodeling. No other techniques such as cranial helmet therapy or endoscopic strip craniectomy were used in any of the children included in this study.

Acute blood losses were substituted by infusion of hydroxyethyl starch (HAES 6%, MW 130 000, Voluven, Fresenius, Bad Homburg) or albumin (human serum albumin 5%, Alburnorm 50g/l, Octapharma, Vienna) according to the assessment of the attending anesthesiologist. The transfusions of PRBC, human plasma, platelets and other blood products were conducted according to the “Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives“, published by the board of the German Medical Association (Bundesärztekammer). PRBCs were always transfused to children with a lower hemoglobin level of 6 g/dl, and never with a higher hemoglobin level of 10 g/dl. Between a hemoglobin level of 6 to 10 g/dl, transfusion was or was not conducted due to the capacity of compensation, symptoms of anemic hypoxia (e.g. tachycardia, hypotension, ECG ischemia, lactacidosis) or ongoing blood loss. There was no significant difference in the lowest hemoglobin level intraoperatively between the control and the verum group (9.2 g/dl vs 7.9 g/dl, n.s.).

In both groups a cell salvage system (Cell Saver 5, Haemonetics Corporation, Massachusetts, USA) was used and, whenever possible, cell salvage blood was re-transfused.

All children were extubated at the end of surgery and transferred for postoperative monitoring to

the pediatric intensive care unit.

The surgical and anesthesia procedures remained the same in both groups for the duration of this study. No changes were made in the use of other hemostatic devices, protocols for blood sparing efforts, fluid management or blood pressure management as well as blood product replacement decisions.

Topical hemostasis

In the control group, bone wax was used after the detachment of the combined subgaleal and pericranial flap from the cranium in order to minimize bleeding from the large and small venae emissariae. In the treatment group, bone wax was used for venae emissariae larger than approximately 2 mm in diameter. However, for the many small venae emissariae, SeraSeal® was used instead of bone wax. There, SeraSeal® was applied in small drops stepwise directly on the cranium, as stated in the instruction leaflet. After that, the place of application was not manipulated for one minute. If no further bleeding occurred, the surgical procedure was pursued. If bleeding from the venae emissariae continued, another application of SeraSeal® took place according to the manufacturer's recommendation. It took two rounds of applying SeraSeal® to control a typical case, requiring five ml of SeraSeal® overall. Never was applying more than two rounds of SeraSeal® necessary in order to control bleeding from the many small venae emissariae.

Data collection

Data were gathered using medical reports such as operative reports, nursing reports and intensive care reports, reports from the blood reservoir and anesthesia logs. We also collected data from the laboratory findings which were analyzed the day before surgery and between the 4th-7th day after surgery. The following data set was collected: demographic data as age, weight, sex ratio, type of craniosynostosis, American Society of Anesthesiologists (ASA) status, laboratory findings, surgical time, anesthesia time, length of hospital stay, postoperative laboratory findings and the volume of blood products and cell salvage blood transfused during and after surgery.

The primary outcome variable was the volume of PRBC transfused during surgery. Secondary outcome variables were the postoperative and total volume of PRBC, human plasma, platelet concentrates, fibrinogen concentrates (Haemocomplettan P, CSL Behring GmbH, Marburg, Germany) and post surgery laboratory values.

Potential adverse events induced by the application of SeraSeal®, such as pruritus, nausea, vomiting, fever, wound infection, thrombotic complications or convulsive seizure, were noted.

Statistical analysis

Statistical analysis was performed in cooperation with the Institute of Medical Informatics, Biostatistics and Epidemiology of the University of Munich, Germany using GraphPad Prism (Version 6.01 2012, © 1992-2012 GraphPad Software, Inc.) and SPSS (version 22.0). We tested Gaussian distribution of every variable with a Kolmogorov-Smirnov test. Because more than 50 percent of them were nongaussian variables and the sample size was small, we compared continuous variables using a Mann-Whitney U test and categorical data using Fisher's exact-test

as appropriate. Continuous data were expressed as median and interquartile range. Categorical data were expressed as frequencies (%). The conducted analyses were two tailed. A significance threshold of $P < 0.05$ was defined.

RESULTS

Baseline characteristics

35 children were enrolled in either the retrospective control group ($n=23$) or prospective verum group ($n=12$). There were no significant differences in age or weight between the two groups. There were also no relevant differences in type of craniosynostosis and preoperative laboratory findings. Detailed baseline characteristics are listed in table 1.

Transfusion Requirements

All of the children in both groups were transfused. However, the volume of intraoperative PRBC transfusion was significantly lower (-44.5% , $p < 0.05$) during the intraoperative period in patients receiving SeraSeal® compared with the control group (see table 2 figure 1). Although there was no significant difference regarding PRBC transfusion during the postoperative period, the volume of PRBC transfusion during the whole study (intra- and postoperative period combined) was reduced significantly by the application of SeraSeal® (-59.3% , $p < 0.05$, see table 2 figure 2).

In the control group, 17 (73.9%) of 23 children received human plasma transfusion compared

with 4 (33.3%) of 12 children in the verum group ($p < 0.05$). There was no significant difference between the amounts of administered fibrinogen concentrates or platelet transfusions. There was also no significant difference between the volumes of retransfused cell salvage blood between both groups and length of hospital stay, whereas surgical time was significantly shorter in the SeraSeal® group.

Children in the verum group received significantly less crystalloids than children in the control group. There was no difference of the amount of colloids administered during surgery between both groups. Since the type of colloid was not prescribed a post hoc regression analysis was performed in order to investigate the influence of the type of colloid (hydroxyethyl starches vs albumin) on the transfusion rate. However, this analysis did not demonstrate any difference between the colloids used.

Postoperative laboratory variables (i.e. haemogram, CRP, differential blood count) were also comparable between the control and verum group. Coagulation parameters weren't measured postoperatively. In the control group, 60mg of tranexamic acid were transfused to one child intraoperatively and 100mg to another child postoperatively. In the verum group, only one child was given 100mg of tranexamic acid.

No adverse events were noted.

Detailed intraoperative and postoperative results are listed in table 2.

DISCUSSION

This study aimed to evaluate whether SeraSeal® as supplement to bone wax has the ability to reduce transfusion requirements in pediatric craniosynostosis surgery. Our key finding was that the amount of PRBC transfusion during surgery and the complete perioperative period was significantly lower in the SeraSeal® group than in the control group.

In the control group the mean amount of perioperatively transfused PRBC was 54 ml/kg, which is comparable to findings in other studies (*Stricker et al.*, 2010, *Goobie et al.*, 2011, *van Uitert et al.*, 2011, *Oppenheimer et al.*, 2014), in contrast to a rate of 25 ml/kg in the SeraSeal® group resulting in a reduction of nearly 54%.

Although there is a large amount of effort to reduce perioperative bleeding during craniosynostosis surgery, significant blood loss and high amounts of PRBC transfusion still frequently occur and interfere with outcome. However, in the last few years the doubts about the benefits of PRBC transfusions increased, since it has been demonstrated convincingly, that the risk – benefit ratio of PRBC transfusion does not seem to be as beneficial as suggested in earlier years (*White et al.*, 2009, *Isbister et al.*, 2011, *van Uitert et al.*, 2011).

We demonstrated that topical application of SeraSeal® during craniosynostosis surgery significantly reduced the need for perioperative transfusion without any severe adverse effects. As a mechanism of action, we propose that the use of SeraSeal® on small venae emissariae, after removal of the pericranium, stopped bleeding more quickly and more sufficiently than bone wax. Therefore blood loss could be minimized, resulting in lower transfusion requirements, estimated to be beneficial according to current scientific knowledge.

To ensure the comparability of the verum and the control group, we compared baseline characteristics of both groups. There were no significant differences between the two groups

regarding most of the relevant parameters. However, we could find that in the SeraSeal® group the operation time, as well as the amount of fluids administered was significantly lower than in the control group, although the same operation technique - cranial vault remodeling – was used in both groups for every type of craniosynostosis.

It can be speculated that both phenomena have a similar explanation: the longer the time course of a surgical procedure, the more extended the concomitant loss of blood will presumably be (*White et al.*, 2009, *Stricker et al.*, 2010, *van Uitert et al.*, 2011). As a consequence, the necessity to substitute blood losses with crystalloids, colloids or even PRBC will very often depend on the duration of the surgical procedure. However, this point of view does not describe causality: one might speculate that the duration of surgical procedures declined due to the increasing practice of the surgical team, since procedures for all patients of the verum group were done after the control group. Whereas others could explain the shorter surgical time due to the action of SeraSeal®, since bleeding from the venae emissariae could be stopped more effectively and as a consequence, surgeons had to deal with hemostasis for a shorter time period.

Regarding the minimization of transfusion rate with the help of SeraSeal® it is very difficult to compare our findings with those of other studies. To our knowledge there are neither studies in craniosynostosis surgery on the use of SeraSeal®, nor comparisons between SeraSeal® and other hemostatic agents so far. Therefore our study can be seen as a hypothesis generating pilot study of this therapeutical approach.

We acknowledge that a topical hemostatic agent, such as SeraSeal®, only contributes a small part in minimizing blood loss in craniosynostosis surgery, but very well finds its rationale in maintaining hemostasis. There are many other, more in depth multifactorial protocols (e.g.

tranexamic acid (*Dadure et al.*, 2011, *Goobie et al.*, 2011, *Maugans et al.*, 2011, *Crantford et al.*, 2015), preoperative erythropoietin (*Helphaer et al.*, 1998, *Fearon and Weinthal*, 2002, *Meneghini et al.*, 2003, *Fearon et al.*, 2014, *Vega et al.*, 2014), acceptance of low hemoglobin levels (*Stricker et al.*, 2012, *Vega et al.*, 2014, *Nguyen et al.*, 2015)) showing promising results in minimizing blood loss and transfusion requirements. However, we think that these concepts are not mutually exclusive and the combination of multifactorial protocols together with reliable topical hemostatic agents, such as SeraSeal®, might be the best concept to maintain meticulous hemostasis.

No side or adverse events were noted in our study. This is of special interest, since we used SeraSeal® in a pediatric population. Although SeraSeal® is approved for the use in children in Austria it has to be noted that SeraSeal® contains bovine proteins, and as a consequence reactions in patients who are allergic to bovine products can occur and could possibly lead to allergic or anaphylactic reactions (*Xerasal*). However, the small number of pediatric patients included in our study does not allow one to deduce a safety profile of SeraSeal®, especially for this population.

Our study has several potential limitations that might limit our conclusions. A possible confounder may be the incoherent use of different colloids in both groups due to the Dear Doctor Letter published on November 12, 2013 strongly limiting the use of hydroxyethyl starch due to safety concerns (*Rasmussen et al.*, 2014). As a consequence hydroxyethyl starch had been used more often in our protocol in the control group than in the verum group. This imbalance of colloid usage might influence the results obtained, however to evaluate the influence of the use of different colloids on the amount of PRBC transfused during operation, we performed an additional regression analysis, which demonstrated that there is no significant relation between

colloid use and intraoperative transfusion requirement in our present study. So the different use of colloids may only have played a minor role in the results obtained by our study.

Although we didn't have a preset transfusion threshold eligible for all children, transfusion triggers were the same in both groups as mentioned before. Furthermore, there were no significant differences in the lowest accepted hemoglobin level during operation between both groups.

CONCLUSION

We acknowledge that our study is relatively small; our study design is associated with certain restrictions, impeding its level of evidence to reach the level of a randomized, controlled blinded study. We understand our trial as hypothesis generating and we suggest the effect of SeraSeal® on transfusion requirements should be assessed prospectively in other studies.

However, our analysis strongly suggests that SeraSeal® has a strong potential to reduce transfusion requirements in pediatric craniosynostosis surgery. As a result, SeraSeal® could be an important contribution and an additional means to reduce the amount of allogeneic blood transfusion requirements in order to improve the outcome of patients not only in craniosynostosis, but also in other fields of surgery.

This study represents part of the thesis to be submitted by the author to obtain a doctoral degree at the Faculty of Medicine of the Ludwig-Maximilians-University Munich.

Acknowledgments

The authors thank M. Nimmervoll, State Women's and Children's Hospital Linz, Austria, for the help in data collection.

Disclosure

Conflicts of interest: none.

No funding was obtained or used for this study.

Informed parental consent was obtained for children in the SeraSeal® group.

Authorship contributions:**Category 1**

Conception and design of study: R. Stehrer, B. Parsaei, M. Malek, M. Jacob, G. Geiselseder, J. Meier

Acquisition of data: R. Stehrer, S. Hunger,

Analysis and/or interpretation of data: R. Stehrer, K.-J. Schotten, M. Malek, M. Jacob, J. Meier

Category 2

Drafting the manuscript: R. Stehrer, M. Malek, J. Meier

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All authors have seen and approved the final version of the manuscript being submitted to JCMFS.

References

Crantford, J. C., B. C. Wood, J. R. Claiborne, D. G. Ririe, D. E. Couture, J. T. Thompson and L. R. David: Evaluating the safety and efficacy of tranexamic acid administration in pediatric cranial vault reconstruction. *J Craniofac Surg* **26**(1): 104-107, 2015.

Dadure, C., M. Sauter, S. Bringuier, M. Bigorre, O. Raux, A. Rochette, N. Canaud and X. Capdevila: Intraoperative tranexamic acid reduces blood transfusion in children undergoing craniostomy surgery: a randomized double-blind study. *Anesthesiology* **114**(4): 856-861, 2011.

Fearon, J. A., T. K. Cook and M. Herbert: Effects of Hypotensive Anesthesia on Blood Transfusion Rates in Craniostomy Corrections. *Plast Reconstr Surg* **133**(5): 1133-1136, 2014.

Fearon, J. A. and J. Weinthal: The use of recombinant erythropoietin in the reduction of blood transfusion rates in craniostomy repair in infants and children. *Plast Reconstr Surg* **109**(7): 2190-2196, 2002.

Goobie, S. M., P. M. Meier, L. M. Pereira, F. X. McGowan, R. P. Prescilla, L. A. Scharp, G. F. Rogers, M. R. Proctor, J. G. Meara, S. G. Soriano, D. Zurakowski and N. F. Sethna: Efficacy of tranexamic acid in pediatric craniostyostosis surgery: a double-blind, placebo-controlled trial. *Anesthesiology* **114**(4): 862-871, 2011.

Helfaer, M. A., B. S. Carson, C. S. James, J. Gates, D. Della-Lana and C. Vander Kolk: Increased hematocrit and decreased transfusion requirements in children given erythropoietin before undergoing craniofacial surgery. *J Neurosurg* **88**(4): 704-708, 1998.

Isbister, J. P., A. Shander, D. R. Spahn, J. Erhard, S. L. Farmer and A. Hofmann: Adverse blood transfusion outcomes: establishing causation. *Transfus Med Rev* **25**(2): 89-101, 2011.

Kimonis, V., J. A. Gold, T. L. Hoffman, J. Panchal and S. A. Boyadjiev: Genetics of craniostyostosis. *Semin Pediatr Neurol* **14**(3): 150-161, 2007.

Maugans, T. A., D. Martin, J. Taylor, S. Salisbury and G. Istaphanous: Comparative analysis of tranexamic acid use in minimally invasive versus open craniostyostosis procedures. *J Craniofac Surg* **22**(5): 1772-1778, 2011.

Meneghini, L., N. Zadra, V. Aneloni, S. Metrangolo, R. Faggin and F. Giusti: Erythropoietin therapy and acute preoperative normovolaemic haemodilution in infants undergoing craniostyostosis surgery. *Paediatr Anaesth* **13**(5): 392-396, 2003.

Nguyen, T. T., S. Hill, T. M. Austin, G. M. Whitney, J. C. Wellons, 3rd and H. V. Lam: Use of blood-sparing surgical techniques and transfusion algorithms: association with decreased blood administration in children undergoing primary open craniostyostosis repair. *J Neurosurg Pediatr*: 1-8, 2015.

Oppenheimer, A. J., K. Ranganathan, B. Levi, J. M. Strahle, J. Kapurch, K. M. Muraszko and S. R. Buchman: Minimizing transfusions in primary cranial vault remodeling: the role of aminocaproic acid. *J Craniofac Surg* **25**(1): 82-86, 2014.

Pietrini, D.: Intraoperative management of blood loss during craniostomosis surgery. *Paediatr Anaesth* **23**(3): 278-280, 2013.

Rasmussen, K. C., P. I. Johansson, M. Hojskov, I. Kridina, T. Kistorp, P. Thind, H. B. Nielsen, B. Ruhnu, T. Pedersen and N. H. Secher: Hydroxyethyl starch reduces coagulation competence and increases blood loss during major surgery: results from a randomized controlled trial. *Ann Surg* **259**(2): 249-254, 2014.

Renier, D., E. Lajeunie, E. Arnaud and D. Marchac: Management of craniostomoses. *Childs Nerv Syst* **16**(10-11): 645-658, 2000.

Stricker, P. A., J. E. Fiadjoe, T. J. Kilbaugh, E. Y. Pruitt, J. A. Taylor, S. P. Bartlett and J. J. McCloskey: Effect of transfusion guidelines on postoperative transfusion in children undergoing craniofacial reconstruction surgery. *Pediatr Crit Care Med* **13**(6): e357-362, 2012.

Stricker, P. A., T. L. Shaw, D. G. Desouza, S. V. Hernandez, S. P. Bartlett, D. F. Friedman, D. A. Sesok-Pizzini and D. R. Jobes: Blood loss, replacement, and associated morbidity in infants and children undergoing craniofacial surgery. *Paediatr Anaesth* **20**(2): 150-159, 2010.

van Uiter, A., J. H. Megens, C. C. Breugem, B. M. Stubenitsky, K. S. Han and J. C. de Graaff: Factors influencing blood loss and allogeneic blood transfusion practice in craniostomosis surgery. *Paediatr Anaesth* **21**(12): 1192-1197, 2011.

Vega, R. A., C. Lyon, J. F. Kierce, G. W. Tye, A. M. Ritter and J. L. Rhodes: Minimizing transfusion requirements for children undergoing craniosynostosis repair: the CHoR protocol. *J Neurosurg Pediatr* **14**(2): 190-195, 2014.

Virchow, R.: Über den Cretinismus, namentlich in Franken und über pathologische Schädelformen. *Verh Phys Med Ges Würzburg* **2**: 230-271, 1851/1852.

White, N., R. Marcus, S. Dover, G. Solanki, H. Nishikawa, C. Millar and E. D. Carver: Predictors of blood loss in fronto-orbital advancement and remodeling. *J Craniofac Surg* **20**(2): 378-381, 2009.

Xerasal: Product Information SeraSeal®. Last accessed: 17.May2016, from <http://www.xerasal.ch/seraseal>.

Zöller, J. and J. Mühling: Kraniofaziale Chirurgie. In: J.-E. Hausamen, E. Machtens, J. F. Reuther, H. Eufinger, A. Kübler and H. Schliephake, *Mund-, Kiefer- und Gesichtschirurgie.*, Springer-Verlag Berlin Heidelberg: 417-438, 2012.

Table 1: Baseline characteristics

Variable	Control group (n=23)	Verum group (n=12)
Male/Female Ratio	18:5	8:4
Age, mo	9.0 (7.0 – 11.5)	9.5 (9.0 – 12.5)
Weight, kg	8.7 (7.8 – 9.8)	8.8 (8.2 – 10.2)
ASA Status, I/II/III	20/3/0	7/4/1
Type of Craniosynostosis†		
Plagiocephaly	3 (13)	1 (8)
Scaphocephaly †	12 (52)	5 (42)
Trigonocephaly	7 (31)	4 (33)
Complex	1 (4)	2 (17)
Preoperative laboratory findings		
Erythrocytes (T/l)	4.6 (4.4 – 5.0)	4.8 (4.4 – 5.0)
Haemoglobin (g/dl)	12.0 (11.5 – 12.4)	11.8 (11.0 – 12.1)
Leucocytes (G/l)	11.4 (8.6 – 13.0)	11.3 (10.0 – 12.0)
Platelets (G/l)	347.0 (308.0 – 377.0)	345.5 (261.5 – 425.5)
Haematocrit (%)	34.8 (32.8 – 36.0)	33.5 (31.7 – 35.3)
Quick (%)	97.0 (85.3 – 107.8)	98.0 (93.0 – 105.0)
INR	1.02 (0.95 – 1.10)	1.02 (0.98 – 1.04)
aPTT (sec)	27.0 (25.3 – 28.0)	25.5 (23.8 – 27.0)
Thrombin time (sec)	16.0 (15.0 – 17.0)*	17.0 (16.8 – 19.0)*
Fibrinogen (mg/dl)	211.5 (169.5 – 227.5)	187.0 (169.0 – 235.0)
CRP (mg/dl)	0.0 (0.0 – 0.10)	0.0 (0.0 – 0.03)

* $p < 0.05$, Data are given as median (interquartile range) unless otherwise indicated.

†Data are given as number (percentage) of each group.

Table 2: Intraoperative and postoperative results

Variable	Control group (n=23)	Verum group (n=12)
Volume of PRBC transfused, ml/kg		
Intraoperatively	40.3 (27.4 – 67.0)*	17.6 (12.1 – 30.5)*
Postoperatively	0.0 (0.0 – 17.01)	0.0 (0.0 – 10.2)
Total	55.4 (32.6 – 73.3)*	23.2 (18.0 – 30.5)*
No of patients receiving human plasma transfusion†		
Intraoperatively	17 (73.9)*	4 (33.3)*
Postoperatively	1 (4.3)	0 (0)
Total	17 (73.9)*	4 (33.3)*
Length of hospital stay, days	8.0 (8.0 – 10.0)	8.5 (8.0 – 9.0)
Surgical Time, min	182.0 (149.0 – 221.0)*	149.0 (122.5 – 169.8)*
Crystalloid Infusion, ml/kg	71.0 (57.5 – 124.1)*	30.93 (24.9 – 58.0)*
Colloid Infusion, ml/kg	0.0 (0.0 – 17.1)	0.0 (0.0 – 9.0)
No of patients with colloid Infusion†		
Intraoperatively	8 (34.8)	5 (41.7)
Thereof patients who received†		

Hydroxyethyl starches	7 (87.5)	1 (20.0)
Albumin 5%	1 (12.5)	4 (80.0)
Cell-salvaged blood re-		
transfused, ml		
Intraoperatively	110.0 (63.0 – 206.0)	65.0 (0.0 – 214.3)
No of patients with fibrinogen		
transfusion†		
Intraoperatively	8 (34.8)	2 (16.7)
Postoperatively	4 (17.4)	2 (16.7)
Total	12 (52.2)	4 (33.3)
No of patients with platelet		
transfusion†		
Intraoperatively	0 (0)	0 (0)
Postoperatively	2 (8.7)	0 (0)
Postoperative laboratory findings		
Erythrocytes (T/l)	4.0 (3.5 – 4.5)	3.9 (3.4 – 4.5)
Haemoglobin (g/dl)	10.9 (9.6 – 12.0)	10.7 (8.3 – 11.8)
Leucocytes (G/l)	9.1 (7.4 – 10.3)	10.6 (8.6 – 11.7)
Platelets (G/l)	289.0 (262.0 – 334.0)	348.5 (253.0 – 398.0)
Haematocrit (%)	32.9 (28.5 – 35.5)	32.2 (24.6 – 34.5)
CRP (mg/dl)	1.4 (0.8 – 3.3)*	0.8 (0.5 – 1.3)*

* $p < 0.05$, Data are given as median (interquartile range) unless otherwise indicated.

† Data are given as number (percentage) of each group.

Captions to Illustrations

Table 1: Baseline characteristics

Imaged are important baseline characteristics of both groups containing general parameters, types of craniosynostosis and preoperative laboratory findings.

Table 2: Intraoperative and postoperative results

Imaged are important intraoperative and postoperative results of both groups containing information about transfusion requirements, fluid management, surgical parameters and postoperative laboratory findings.

Figure 1: Intraoperative PRBC Transfusion

Scatterplot; each dot indicates the volume of PRBCs in ml transfused to a child of the control group, each square indicates the volume of PRBCs in ml transfused to a child of the verum group where SeraSeal® was used. Only the volume of transfused PRBCs in the intraoperative period was considered.

Figure 2: Total PRBC Transfusion

Scatterplot; each dot indicates the volume of PRBCs in ml transfused to a child of the control group, each square indicates the volume of PRBCs in ml transfused to a child of the verum group where SeraSeal® was used. The volumes of transfused PRBCs during operation and during the postoperative period together were considered.

