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

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ABSTRACT

Background and objectives: Craniosynostosis surgery is often associated with severe perioperative bleeding especially due to venae emissariae, resulting in large transfusion amounts of packed red blood cells (PRBCs). Blood loss from venae emissariae is usually reduced by the usage of bone wax. SeraSeal is a new hemostatic agent which might help to reduce transfusion amounts if used additionally to bone wax.
Materials and methods: This study was designed with a retrospective control group (23 children), treated only with bone wax and a consecutive prospective verum group (12 children) treated additionally with SeraSeal. All children solely suffered from non-syndromic craniosynostosis, and were all treated by the same surgeons. Primary outcome variable was the volume of PRBC transfused during surgery.
Results: The numbers of PRBC transfusion was reduced significantly during the intraoperative period in the SeraSeal group (−44.5%, $p < 0.05$) and also during the combination of the postoperative and intraoperative period (−59.3%, $p < 0.05$).
Conclusion: Our analysis suggests that SeraSeal has a strong potential to reduce transfusion requirements in pediatric craniosynostosis surgery. However, we acknowledge that due to small numbers our trial can only be seen as hypothesis generating pilot study. We suggest that the effect of SeraSeal should be assessed prospectively in other studies.

1. 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 3–5 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

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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 craniosynostosis (Xerasal). However, efficacy of SeraSeal® to reduce perioperative bleeding in the setting of craniosynostosis 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 craniosynostosis surgery.

2. Material and methods

2.1. 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 craniosynostosis 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 craniosynostosis, 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.

2.2. 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 were set to maintain normocapnia. Anesthesia 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 45–65 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%, Albunorm 50 g/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 6–10 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.

2.3. 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 1 min. 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 milliliters of SeraSeal® overall. Never was applying more than two rounds of SeraSeal® necessary in order to control bleeding from the many small venae emissariae.

2.4. 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