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The Enhanced Recovery After Surgery protocol for the surgical management of craniosynostosis: Lausanne experience

Amani Belouaer, MD,[1] Giulia Cossu, MD,[1] Soulayma Al-Tayyari,[1] Adela Bubenikova,[2] Catalina Caliman, BSc,[1] Fabio Agri, MD,[3] Maria-Helena Perez, MD,[4] Vivianne Chanez, MD,[4] Yann Boegli, MD,[5] Caroline Mury, MD,[5] Roy Thomas Daniel, MD,[1] and Mahmoud Messerer, MD[1]

[1]Department of Clinical Neuroscience, Service of Neurosurgery, Lausanne University Hospital and University of Lausanne, Switzerland; [2]Department of Neurosurgery, 2nd Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic; [3]Department of Administration and Finance, Lausanne University; [4]Department of Pediatrics, Pediatric Intensive and Intermediate Care Units, Women-Mother-Child Department, Lausanne University Hospital and University of Lausanne; and [5]Department of Anesthesiology, Pediatric Unit, Lausanne University Hospital and University of Lausanne, Switzerland

OBJECTIVE Over the past decade, the Enhanced Recovery After Surgery (ERAS) program has demonstrated its effectiveness and efficiency in improving postoperative care and enhancing recovery across various surgical fields. Preliminary results of ERAS protocol implementation in craniosynostosis surgery are presented.

METHODS An ERAS protocol was developed and implemented for cranial pediatric neurosurgery, focusing on craniosynostosis repair. The study incorporated a pre-ERAS group consisting of a consecutive series of patients who underwent craniosynostosis repair surgery prior to the implementation of the ERAS protocol; the results were compared with a consecutive group of patients who had been prospectively collected since the introduction of the ERAS for craniosynostosis protocol. The safety, feasibility, and efficiency of the ERAS protocol in pediatric neurosurgery was evaluated, through the collection of clinical data from the pre-, intra-, and postoperative phase. Surgery-related complications were evaluated according to the Clavien-Dindo classification. Costs of the stays were obtained using a microcosting approach.

RESULTS A total of 35 pre-ERAS patients and 10 ERAS patients were included. Scaphocephaly was the most common pathology in both groups. The overall compliance with the pre-, intra-, and postoperative criteria significantly increased—from 35.5%, 64.4%, and 54.7%, respectively, in each phase to 94%, 90%, and 84% ($p < 0.001$). The authors noticed a reduction in the average opioid dose used per patient in the ERAS group ($p = 0.004$), and they observed a trend toward a decreased mean length of stay from 5.2 days in the pre-ERAS group to 4.6 days in the ERAS group, without an increase of the rate of readmission within 30 days of surgery. The rate of complications decreased but this difference was not statistically significant. The hospital costs lowered significantly: from 21,958 Confederatio Helvetica Francs (CHF) in the pre-ERAS group to 18,936 CHF in the ERAS group ($p = 0.02$).

CONCLUSIONS The ERAS protocol represents a safe and cost-effective tool for the perioperative management of craniosynostosis. It showed its positive impact on the analgesia provided and on the reduction of in-hospital costs for these patients. ERAS protocols may thus be interesting options in the pediatric neurosurgical field.

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KEYWORDS Enhanced Recovery After Surgery; ERAS; craniosynostosis; neurosurgery; pediatric

The implementation of the Enhanced Recovery After Surgery (ERAS) program has proven to be effective in improving postoperative recovery and reducing stress response to surgery.[1–3] The ERAS Society published its first guidelines in adult colorectal surgery in 2005,[4] and since then 26 ERAS guidelines and consensus statements have been published in the last decade.[5–30] ERAS implementation resulted in significant improvements in patient care, and in reduced complications and length of stay (LOS) in different surgical specialties.[21,31,32] Despite these successes, there are few cranial neurosurgical and pediatric ERAS studies, and there are currently no ERAS

ABBREVIATIONS CBC = complete blood count; CHF = Confederatio Helvetica Francs; ERAS = Enhanced Recovery After Surgery; FLACC = face, legs, activity, cry, consolability; ICU = intensive care unit; IMCU = intermediate care unit; IV = intravenously; LOS = length of stay; PONV = postoperative nausea and vomiting.

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Society cranial neurosurgical guidelines. The only ERAS Society pediatric guidelines were published for neonatal intestinal surgery.[7]

Between April 2022 and June 2023, and under the aegis of the ERAS Society, our department of neurosurgery developed two ERAS protocols,[33] and one of them was dedicated to craniosynostosis repair. During this period of implementation, we validated our local protocol for ERAS for craniosynostosis, defined the compliance criteria, and developed the patient booklet (Online Appendix 1). As a result of this process, our department was certified by the ERAS Society.

Craniosynostosis represents a congenital anomaly characterized by premature fusion of cranial bones during early stages of a newborn's skull development, prior to the completion of brain growth. Therefore, this anomaly leads to cranial deformity and detrimental impacts on neurocognitive development. A fundamental factor in the management of these patients is the collaboration among the different teams involved in patient care. Lack of consistent communication among neurosurgeons, pediatricians, intensive care teams, anesthesiologists, and parents can lead to critical information being overlooked. Consequently, this may result in delayed initiation of refeeding and mobilization, or even inappropriate management approaches.

The aim of this paper was to describe our ERAS for craniosynostosis protocol and to report our preliminary results in terms of compliance, complications, LOS, and costs before and after implementation of the protocol.

Methods

Multidisciplinary Team

The ERAS for craniosynostosis team included 12 active members: 3 neurosurgeons, 2 pediatric intensive care physicians, 2 pediatric anesthesiologists, 4 clinical nurses, and 1 ERAS nurse coordinator. All the members participated in the certification process, and they contributed to the design and implementation of the ERAS for craniosynostosis protocol.

ERAS for Craniosynostosis Protocol

Based on ERAS recommendations for pediatric and adult patients,[2,7,34] the ERAS for craniosynostosis protocol (Online Appendix 2) included three phases—namely the pre-, intra-, and postoperative phases. Our multidisciplinary team performed a literature review to adhere to the best current recommended clinical practice in the surgical management of patients with craniosynostosis.

Preoperative Phase

During the neurosurgical consultation, the surgeon explained the type of craniosynostosis, the surgical technique, and the information on helmet use in the postoperative period, as well as the risks of surgery. Bone imaging (CT scan) was performed to visualize the suture fusion and plan the surgery, and a genetic consultation was recommended to the parents. A consultation with the ERAS nurse allowed preoperative education and counseling of the parents. We also proposed a guided tour of the intensive care unit (ICU) and the intermediate care unit (IMCU) to the parents, as well as the standard pediatric neurosurgery unit, to familiarize them with the environment and reduce their stress.[35] We also explained the usefulness of early feeding and early mobilization. An anesthesiology consultation was performed in the outpatient clinic and repeated the day before surgery.

Intraoperative Phase

Blood group testing was performed and blood products were ordered during anesthesia induction. A central venous catheter was used only if two peripheral venous lines were not possible. An arterial line and urinary catheter with output measurement were inserted. The mean arterial pressure was set at a minimum of 50 mm Hg with minimal diuresis of 1 ml/kg/hr. Body temperature was maintained between 36.5°C and 37.5°C during the entire surgery. Antibiotic therapy was administered 30 minutes before surgical incision. Tranexamic acid was administered according to the protocol, namely 10 mg/kg intravenously (IV) over 10 minutes, followed by a maintenance dose of 5 mg/kg/hr until the end of the surgery.

All the procedures in both groups were performed by the senior pediatric neurosurgeon (M.M.). All the patients were positioned supine on an air mattress that allows for proper head support in a neutral position with head flexion at 20°, along with elevation of the shoulders and the lower part of the body. An open vault remodeling procedure using Renier's "H" craniotomy method was used for scaphocephaly,[36] whereas patients who were surgically treated before the age of 4 months underwent an endoscopic procedure. Patients with anterior plagiocephaly, trigonocephaly, and brachycephaly underwent open surgeries to remove the affected suture, and reshaping of the anterior half of the convexity was performed from the coronal suture to the orbital rim in collaboration with a maxillofacial surgical team.[37]

The skin incision was a unique bicoronal zigzag incision for all open surgeries. For endoscopic approaches, patients had one anterior 5-cm linear incision along the coronal suture just behind the anterior fontanelle and one incision posterior to the lambdoid sutures. The subcutaneous plane was infiltrated before skin incision by using 1% lidocaine with 10 μg/ml epinephrine to minimize cutaneous bleeding, without exceeding the dose of 7 mg/kg. Skin incisions were closed with a lock-stitch cutaneous suture by using an absorbable suture. Drains were used only for open procedures.

Postoperative nausea and vomiting (PONV) were handled by administering methylprednisolone 0.1 mg/kg IV at the beginning of the procedure and ondansetron 0.1 mg/kg IV 30 minutes before the end of the procedure. To control postoperative pain, we administered paracetamol 15 mg/kg IV 30 minutes before the end of the procedure and morphine 0.1 mg/kg IV 20 minutes before the end of the procedure.

Postoperative Phase

Pain was evaluated within 1 hour after ICU or IMCU admission using the face, legs, activity, cry, consolability (FLACC) score, which is validated for preverbal children in pain after surgery.[38,39] Patient mobilization was per-

TABLE 1. Compliance criteria selected for the ERAS for craniosynostosis protocol

Preop Criteria	Intraop Criteria	Postop Criteria
Confirmation of Dx after cranial CT scan	Blood type testing performed before incision	Postop analgesia according to protocol
Genetics counseling	2 peripheral venous access or 1 central venous access	Arterial catheter withdrawal in recovery room if transfer to IMCU
Preanesthetic consultation	Arterial catheter	Arterial catheter withdrawal on POD1 if transfer to ICU
ERAS nurse counseling	Bladder catheter at start of surgery	Pain assessment w/ FLACC score w/in 1 hr of arrival at ICU/IMCU
Fasting time respected	Temp btwn 36.5°C & 37.5°C during entire surgery	CBC at 12 hrs postop
	Antibiotic prophylaxis	CBC at 24 hrs postop
	Tranexamic acid 10 mg/kg IV, bolus over 10 mins	Mobilization of child w/in 4 hrs postop
	PONV prophylaxis	Feeding w/in 4 hrs postop
	Arterial blood gas analysis every hr during surgery	Subgaleal drain (if placed) withdrawal at 24 hrs
	Diuresis monitoring	Bladder catheter withdrawal at 24 hrs postop
	Subcutaneous infiltration along scalp incision w/ 1% lidocaine w/ 10 μg/ml epinephrine w/o exceeding the toxic dose of 7 mg/kg	Wound dressing removal at POD3
	Suture of skin incisions w/ a lock-stitch suture using an absorbable 4.0 Vicryl Rapid	Discharge on POD3 after endoscopic surgery
		Discharge on POD5 after open surgery

Dx = diagnosis; POD = postoperative day; temp = temperature.

formed within 4 hours after surgery, along with feeding. A complete blood count (CBC) was performed 12 and 24 hours after surgery. Urinary catheter and subgaleal drains (if present) were withdrawn 24 hours after surgery. All the wounds were left exposed at day 3 after surgery.

Hospital discharge was dependent on the type of intervention; patients undergoing endoscopic repair were discharged on the 3rd day, whereas those having open surgery were discharged on day 5.

To enable easy-to-use communication and collect health surveys twice per day during the 1st week after discharge, with the aim to detect any complication, a smartphone application was developed (CHUV@home). During the first 10–14 days after surgery, the ERAS nurse called the parents to ask about the condition of their child.

Checklist

A checklist was formulated to evaluate the adherence to the protocol and to measure our compliance with it (Table 1). For each indicator, the compliance was calculated as the proportion of patients respecting the criterion divided by the total number of patients included in the analysis. In cases with missing data, the data were recorded as noncompliant. The ERAS certification process was a crucial aspect of the implementation and required compliance metrics ≥ 70% after implementation. Furthermore, we computed the compliance per patient, which represents the ratio of the number of ERAS protocol criteria the patient is adhering to, divided by the total number of criteria.

Outcomes

Between January 2019 and March 2022, we retrospectively reviewed all nonsyndromic patients who underwent craniosynostosis repair surgery, and we included them in the pre-ERAS group. We compared this group with the one treated after the implementation of our ERAS for craniosynostosis protocol, between October 2022 and June 2023 (ERAS group). We analyzed compliance rates, LOS, opioid use, complications, costs, and 30-day readmission rates.

Complications were classified according to the Clavien-Dindo classification of surgical complications.[40,41] A FLACC score ≥ 4 was considered to be a minor complication because this is considered the threshold for opioid administration. A cost analysis was performed from a healthcare provider's perspective to evaluate savings per patient. All costs attributed to resource consumption during the hospital stay, including housing and administrative costs, were assessed using a microcosting approach.[42]

Statistical Analysis

Data were abstracted from the electronic medical record and stored in a REDCap database. To assess the distribution of the data, the Kolmogorov-Smirnov test was used. For comparing categorical variables such as compliance and complication rates between the groups, Fisher's exact test was conducted. For continuous variables like costs, LOS, and age, a t-test was used. A p value < 0.05 was considered indicative of a significant difference. All analyses were carried out using the statistical software package Stata version 16 (StataCorp LLC).

Results

The pre-ERAS group included 35 patients, with an average age of 5.57 ± 2.99 months and a slight male predominance (65.7%). The ERAS group included 10 patients (age

TABLE 2. Demographic information of both cohorts

	Pre-ERAS Group	ERAS Group	p Value
No. of patients	35	10	
Age in mos, mean ± SD	5.57 ± 2.99	4.9 ± 2.91	0.27
Sex, no. (%)			
Males	23 (65.7)	5 (50.0)	0.47
Females	12 (34.3)	5 (50.0)	
LOS in days, mean ± SD	5.23 ± 1.49	4.6 ± 1.11	0.11
ICU/IMCU LOS in days, mean ± SD	1.23 ± 1.26	1.6 ± 1.49	0.22
Type of craniosynostosis, no. (%)			
A) Endoscopic surgery			0.72
Scaphocephaly	14 (40.0)	5 (50.0)	
B) Open surgery			0.47
Scaphocephaly	7 (20.0)	1 (10.0)	
Trigonocephaly	7 (20.0)	1 (10.0)	
Anterior plagiocephaly	6 (17.1)	0 (0.0)	
Brachycephaly	1 (2.9)	3 (30.0)	

4.9 ± 2.91 months). The two cohorts were similar from an epidemiological point of view, and scaphocephaly was the most common diagnosis (60% of cases in both the ERAS and pre-ERAS groups). The rate of open and endoscopic surgeries performed was similar between the two cohorts (40% and 50% in the pre-ERAS and ERAS groups, respectively; $p = 0.72$). Table 2 details demographic and clinical data.

The compliance with the ERAS for craniosynostosis protocol including the pre-, intra-, and postoperative criteria significantly increased from 35.5%, 64.4%, and 54.7%, respectively, to 94%, 90%, and 84% ($p < 0.001$). The compliance of each patient with the local ERAS protocol criteria also increased significantly between the pre-ERAS and the ERAS groups, from 53.4% to 86.5%, respectively ($p < 0.001$). The most important changes occurred in the postoperative management, because we were more attentive to performing early refeeding and mobilization within 4 hours after surgery (Table 3).

We reported a significant reduction in the average opioid dose used per patient from 0.78 ± 0.39 mg/kg to 0.39 ± 0.3 mg/kg in the pre-ERAS and ERAS groups, respectively ($p = 0.004$), with no changes in the FLACC pain score. A nonsignificant trend toward less postoperative pain was even observed in the ERAS group. Also, we observed a nonsignificant reduction in the average duration of opioid use from 2.82 ± 1.64 days in the pre-ERAS group to 2 ± 1.44 days in the ERAS group ($p = 0.1$). The rate of minor and major complications was similar between the two cohorts (Table 4).

The mean LOS slightly decreased from 5.23 days in the pre-ERAS group to 4.6 days in the ERAS group ($p = 0.11$), whereas the average LOS at the IMCU or ICU increased in the ERAS group by 0.23 days ($p = 0.22$). One patient had to be readmitted within 30 days after discharge in the pre-ERAS group for a superficial infection of the surgical wound that needed antibiotic therapy. No readmission was performed in the ERAS group. The preliminary results of our cost-analysis showed a significant reduction of hospitalization costs in the ERAS group. In the pre-ERAS group, the hospital average cost per patient was 21,958 ± 3,142 Confederatio Helvetica Francs (CHF), whereas it dropped significantly to 18,936 ± 4,005 CHF in the ERAS group ($p = 0.029$).

Discussion

The safety, feasibility, and efficiency of the introduction of ERAS protocols in pediatric surgery has been validated.[43–49] These studies reported a significant decrease of the postoperative opioid intake, time to regular diet, time to intravenous fluid discontinuation, intraoperative fluid volume, LOS, and finally in the total costs when applying ERAS protocols.[43–49] This supports the fact that the introduction of ERAS protocols improves patient recovery after surgery without increasing the incidence of complications, the readmission rate, or the financial burden on the hospital.[50]

Despite these encouraging results, there is a significant lack of data on ERAS application in pediatric neurosurgical practice. The only study in the literature reporting the application of the ERAS program for patients with craniosynostosis was the one by Wu et al.[51] They described no decrease in hospital costs or length of hospitalization but they did not detail the protocol they used and they did not report any rate of compliance with their protocol criteria. Nevertheless, the compliance rate is one of the most decisive parameters of ERAS protocol that reflects the efficacy of the application of the protocol itself. Our team showed that we were efficient in adhering to the ERAS for craniosynostosis protocol including the pre-, intra-, and postoperative criteria (94%, 90%, and 84%, respectively, in each phase). During the preoperative phase, the compliance particularly increased in the use of the cranial CT scan and genetics counseling, as we introduced these interventions in accordance with the literature recommendation.[52] The ERAS nurse counseling was also a key factor in the improvement of preoperative management, because it helped in family involvement in treatment decisions, facilitating the understanding of their children's pathology and treatment and thereby increasing their compliance and satisfaction.[53,54]

We also significantly increased our compliance with fasting time, tranexamic acid administration, and PONV prophylaxis. However, this improvement may be biased by the lack of information in the patients' medical record in the pre-ERAS group. One of the important criteria we actively sought to improve was the compliance in maintaining the patient's temperature between 36.5°C and 37.5°C during surgery. Maintaining a consistent body temperature in pediatric patients, particularly during the equipment phase, is challenging. However, we significantly improved our compliance (pre-ERAS group: 8.6%, vs ERAS group: 40%; $p = 0.033$) through the maintenance of the operating room temperature at 30°C–32°C, the use of a warming blanket and heat lamp, and through the administration of warmed intravenous fluids. The compliance during the postoperative phase was lower (84%) when compared to the pre- and intraoperative phase, and this could be at-

TABLE 3. Demonstration of compliance with the ERAS for craniosynostosis protocol during time

Criteria	Pre-ERAS Group (%)	ERAS Group (%)	p Value
Preop			
Confirmation of Dx after cranial CT scan	**11.4**	**100**	**<0.00001**
Genetics counseling	**8.6**	**90**	**<0.00001**
Preanesthetic consultation	100	100	>0.99
ERAS nurse counseling	**0**	**80**	**<0.00001**
Fasting time respected	**57.1**	**100**	**0.018**
Intraop			
Blood type testing performed before incision	88.6	80	0.60
2 peripheral venous access or 1 central venous access	100	100	>0.99
Arterial catheter	97.1	100	0.57
Bladder catheter at start of surgery	85.7	100	>0.99
Temp maintenance btwn 36.5°C & 37.5°C during entire surgery	**8.6**	**40**	**0.033**
Antibiotic prophylaxis	100	100	>0.99
Tranexamic acid 10 mg/kg IV, bolus over 10 mins	**0**	**80**	**<0.00001**
PONV prophylaxis	**11.4**	**100**	**<0.00001**
Arterial blood gas analysis every hr during surgery	91.4	100	>0.99
Diuresis monitoring	88.6	90	>0.99
Subcutaneous infiltration along scalp incision w/ 1% lidocaine w/ 10 μg/ml epinephrine w/o exceeding toxic dose of 7 mg/kg	0	100	**<0.00001**
Suture of skin incisions w/ a lock-stitch suture using absorbable 4.0 Vicryl Rapid	100	100	>0.99
Postop			
Postop analgesia according to protocol	**0**	**100**	**<0.00001**
Arterial catheter withdrawal in recovery room if transfer to IMCU	100	100	>0.99
Arterial catheter withdrawal on POD1 if transfer to ICU	84.6	100	>0.99
Pain assessment w/ FLACC score w/in 1 hr of arrival at care unit	80	70	0.67
CBC at 12 hrs postop	88.6	90	>0.99
CBC at 24 hrs postop	88.6	90	>0.99
Mobilization of child w/in 4 hrs postop	43.8	60	0.48
Feeding w/in 4 hrs postop	48.6	60	0.72
Subgaleal drain (if placed) withdrawal at 24 hrs	84.6	100	0.56
Bladder catheter withdrawal at 24 hrs postop	77.1	80	>0.99
Wound dressing removal at POD3	54.3	80	0.27
Discharge on POD3 after endoscopic surgery	14.2	70	0.08
Discharge on POD5 after open surgery	**0**	**60**	**0.0038**
Postop analgesia according to protocol	52.4	100	0.12

Boldface type indicates statistical significance.

tributed to the fact that more stakeholders were implicated in patients' management in this phase, when compared to the preoperative and intraoperative phase, where a main role is played by the surgeon and the anesthesiologist. In this stage the role of the ERAS nurse is even more important, because he/she is the key to coordinating the different members of the team and maximizing the adherence to the protocol.

To achieve a good rate of compliance, we needed cooperation within the healthcare teams.[53,54] A promising factor to promote ERAS protocol implementation and increase compliance was the development of a mobile-enabled communication.[55]

The rate of complications in the ERAS group seems to decrease in comparison with the pre-ERAS group, even though the small sample analyzed precluded the detection of significant differences. The rate of complications in our series is in line with what is reported in the literature.[56,57] It is relevant to emphasize that we did not encounter any anemia in the ERAS group. The systematic administration of tranexamic acid was associated with a reduction in blood loss and transfusions in the literature,[58] and our adherence to the whole ERAS protocol helped in limiting the incidence of anemia in our group of patients.

Thanks to the introduction of our ERAS for craniosynostosis protocol in the daily clinical practice, we were able to obtain a significant decrease in the average opioid dose per patient. This can be explained by the systematic use of

TABLE 4. Summary of reported surgery-related complications for both groups

Complication	Pre-ERAS Group, No. (%)	ERAS Group, No. (%)
Minor complication (I–IIIa)	17 (48.5)	3 (30)
Wound infection	1 (2.9)	0
Venous thrombosis	1 (2.9)	0
Anemia	2 (5.7)	0
Dural tearing	1 (2.9)	0
Local hematoma	0	1 (10)
FLACC ≥4	12 (34.3)	2 (20)
Major complication (IIIb–V)	5 (14.3)	1 (10)
Symptomatic anemia*	4 (11.4)	1 (10)
Laryngospasm	1 (2.9)	0

* Anemia was considered symptomatic when the patient presented in association with a low hemoglobin value, signs of hemodynamic instability (such as tachycardia or hypotension), and/or dyspnea.

the FLACC pain scale and by the optimization of postoperative analgesic treatment.

A nonsignificant increase in LOS at the IMCU or ICU was reported in the ERAS group, and this could be secondary to the complication we had in this cohort—namely a subcutaneous hematoma needing surgical evacuation. The reported rate of postoperative hematoma in the literature is between 1% and 2%.[56,57] This rate remains consistent with the overall rate (0.9%) of postoperative hematoma for the same surgeon when considering the current series of 45 patients and the one previously published in 2023.[37]

Our study showed a significant difference regarding cost minimization in the ERAS group (18,936 CHF) compared to the pre-ERAS group (21,958 CHF) ($p = 0.029$). The mean reduction of 3,000 CHF per case in the ERAS group, representing an overall real savings of 50,000 CHF/year (considering an average of 17 patients/year treated surgically for craniosynostosis), is a significant amount of money spared for the hospital. One explanation may be that all the patients in our pre-ERAS group spent at least 1 night at the ICU and then were transferred to the IMCU or standard care unit. Since implementation of the ERAS for craniosynostosis protocol, patients undergoing the endoscopic approach went directly to the IMCU. Studies dealing with the application of ERAS in pediatric surgery provide similar cost reductions after ERAS implementation.[7,43,47,48,59] The present work confirms therefore the cost-effective character of the protocol.

This study presents multiple limitations secondary to its retrospective nature and to the small number of patients included in the analysis. Furthermore, it could be argued that in the pre-ERAS era the protocol was not yet present and thus the compliance calculation could be biased. However, a compliance evaluation can be useful to assess the changes in patients' management and to quantify the adherence to some simple criteria that were supposed to be part of the clinical management even before ERAS implementation. Larger cohorts and multicenter studies will be helpful to support the promising results of this paper.

Conclusions

This study provides a framework for the implementation of ERAS protocols in pediatric neurosurgery, while demonstrating the safety and cost-effectiveness of this pathway. Less opioid use and potentially shorter in-hospital stays, along with reduced costs, strongly support the application of a standardized ERAS management for the perioperative care of children with neurosurgically treated pathologies.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Messerer, Belouaer, Cossu, Al-Tayyari, Bubenikova, Caliman, Boegli, Mury. Acquisition of data: Messerer, Belouaer, Al-Tayyari, Caliman, Agri, Perez, Boegli. Analysis and interpretation of data: Messerer, Belouaer, Cossu, Al-Tayyari, Bubenikova, Agri, Mury, Daniel. Drafting the article: Messerer, Belouaer, Cossu, Al-Tayyari, Bubenikova, Daniel. Critically revising the article: all authors. Reviewed submitted version of manuscript: Messerer, Belouaer, Cossu, Al-Tayyari, Agri, Perez, Boegli, Mury, Daniel. Approved the final version of the manuscript on behalf of all authors: Messerer. Statistical analysis: Messerer, Belouaer, Cossu, Al-Tayyari, Agri. Administrative/technical/material support: Belouaer, Caliman. Study supervision: Messerer, Cossu, Daniel.

Supplemental Information

Online-Only Content

Supplemental material is available online.

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Correspondence

Mahmoud Messerer: University Hospital of Lausanne and University of Lausanne, Switzerland. mahmoud.messerer@chuv.ch.