Handling Section Editor: Dr Susan Goobie

Enhanced Recovery After Surgical Correction of Adolescent Idiopathic Scoliosis.

Short Title: ERAS for scoliosis in children

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Clinical Implications

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A. Few studies have been dedicated to the implementation and results of enhanced recovery after surgery experiences during scoliosis surgery
B. The current study finds ERAS to decrease the duration of postoperative hospital stay
C. ERAS after surgery in children can be implemented during major surgeries in children

Abstract

Background: Few publications in the literature examine enhanced recovery after scoliosis surgery (ERAS) in children, despite significant scientific interest in adults. The objective of the current study was to describe an ERAS protocol for surgical correction of adolescent idiopathic scoliosis (AIS) and its results.

Methods: ERAS outcomes were measured in two patient cohorts. Historical controls and ERAS groups were selected from patients managed for scoliosis surgery in 2015 and 2018, respectively. The ERAS protocol included fasting minimization, carbohydrate loading, the avoidance of background morphine infusions, perioperative opioid-sparing protocols, the use of a cooling brace, early physiotherapy, feeding and oral medications, and the early removal of urinary catheters and surgical drains. The main outcome of the study was hospital length of stay.

Results: Overall, 82 controls and 81 ERAS patients were recruited. ERAS protocols were observed in over 80% of patients for almost items. Median length of hospital stay was significantly lower in the ERAS group, (-3 [95% confidence interval: -2; -4] days). Median morphine consumption was reduced by 25% and 35% on day 2 and 3, respectively. The incidence of PONV did not differ between the two groups and the incidence of constipation decreased slightly but significantly in the ERAS group on day 2. Pain intensity at rest and movement were lower in the ERAS group at day 2 and 3.

Conclusions: The current study suggests an ERAS protocol post adolescent idiopathic scoliosis surgery is associated reduced hospital length of stay and improved postoperative care.

Introduction

Recent evidence suggests that ERAS might also be suited to pediatric surgery (1, 2) and might, as previously demonstrated in adults, have beneficial effects in terms of recovery, hospital length of stay (HLOS) and overall quality of care (3, 4).
Scoliosis surgery is a major surgical procedure in pediatrics (5, 6), and the postoperative period is often very challenging. Intense postoperative pain and high postoperative opioid consumption (5, 6) result in high incidences of nausea, vomiting, constipation and urinary retention. Early efficacious physiotherapy is frequently hindered by pain and analgesic side effects. In addition, cognitive impairment, chronic anxiety and/or depression associated with scoliosis can represent significant obstacles to rapid recovery (7). Chronic pain is common following surgery (8, 9), high doses of opioids are frequently required (5, 10) and opioid misuse is of concern (11, 12).

Major advances have been made in addressing these complications: sophisticated preoperative pain management, the treatment of anxiety and depression where present, postoperative pain prevention using perioperative gabapentin (2, 6, 13, 14) or intraoperative dexmedetomidine (15), the use of balanced analgesia combining non-opioid analgesics (especially non-steroidal anti-inflammatory drugs) (16, 17), the use of single or double epidural analgesia (18), and the prevention of nausea, vomiting and constipation (19). However, taken in isolation these measures remain insufficient (20) and multiple targets enhancement such that performed during ERAS might potentially represent a very pertinent intervention in scoliosis surgery patients.

The main goal of the present study was to evaluate the effect of an ERAS protocol on the hospital length of stay after adolescent idiopathic scoliosis (AIS) surgery. Secondary outcomes were: ERAS items observation, opioid consumption, opioids side effects (constipation, nausea and vomiting), pain intensity and postoperative wound infection within 30 days from surgery.

**Material and Methods**

This retrospective monocentric observational study was performed on patients’ data operated from January 2015 to December 2015 and from January 2018 to December 2018, at Robert Debré Teaching hospital in Paris. Both cohorts were selected from our local database of patients managed for scoliosis surgery in our center. The study was IRB approved - Comité d’Evaluation de l’Éthique des projets de Recherche Biomédicale (CEERB) Robert Debré; # 2019/453: Dr Sophie GUILLEMIN-CREPON. Informed consent was waived from the ethical committee given the retrospective nature of the study.

*Inclusion and exclusion criteria*
The inclusion criteria selected patients aged <18 years of age, ASA status 1 to 3, and surgical correction of adolescent idiopathic scoliosis. Exclusion criteria were the following: refusal of study participation and/or personal data use, non-idiopathic scoliosis, contraindication to any commonly used perioperative drug and ASA status 4 or higher.

ERAS protocol

In early 2016, an ERAS protocol was written and approved by a task force including surgeons, anesthesiologists, pediatricians, pain team members, surgical ward nurses, post-anesthetic care unit nurses, physiotherapists and hospital management. Published ERAS literature (21, 22) and French ERAS Group (23, 24) recommendations were the principal sources of inspiration. The protocol’s main features included: fasting minimization, preoperative clear-liquid carbohydrate loading, multimodal analgesia including paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) (17, 25) and nefopam (16), the avoidance of continuous background morphine infusions with patient-controlled analgesia, opioid-sparing protocols aiming to reduce opioid-induced hyperalgesia (10, 15, 16, 26) including gabapentin immediately before surgery and for five days postoperatively (6, 27) and intraoperative dexmedetomidine and ketamine, standardized prevention and treatment of postoperative nausea and vomiting (PONV) (19, 28), antibioprophylaxis (29-32), strict perioperative temperature control and indexed stroke volume guided intravenous fluid protocols (33), rapid physiotherapy, rapid feeding including oral medication as soon as possible postoperatively and the rapid removal of urinary catheters and surgical drains (3, 4, 22, 34).

In practice, a number of ERAS protocol items were standard practice before implementation of the protocol. Significant changes following the introduction of the protocol included (Annex 1):

1. Preoperatively: a formal information about the ERAS protocol and its goals
2. Intraoperatively: intraoperative dexmedetomidine and ketamine
3. Postoperatively (a) the avoidance of continuous background morphine infusions with patient-controlled analgesia, (b) the application of pharmacological and non-pharmacological opioid-sparing techniques (cooling brace) (c) rapid physiotherapy (d) rapid feeding including oral medication as soon as possible and the (e) rapid removal of urinary catheters and (f) rapid removal of surgical drains. All these measures will be described further in the results section.
The full ERAS protocol is displayed in annex 1. Following consensus between members of the task-force, monthly meetings were scheduled over the second half of 2016, preparing members of surgical, medical and paramedical teams for the protocol, its goals and expected benefits for patients. The protocol was then introduced in May 2017. After further consultation, a cooling brace added to the protocol in January 2018 as non-pharmacological analgesia (35). Given the above sequence of events, historical controls were selected from the 2015 calendar year and the ERAS group from 2018.

Anesthesia and perioperative medicine protocol

Perioperative assessments and treatment were standardized and unchanged in both groups. As previously published, all IAS patients in both groups received recombinant erythropoietin (rEPO) and a systematic iron supplementation preoperatively where required (if preoperative hemoglobin concentration was < 14 g.dl⁻¹) to achieve a hemoglobin concentration between 14 and 15 g.dl⁻¹ (33). All patients also received Gabapentin preoperatively (800 mg orally) and over the first five postoperative days (400 mg/day) (6, 27). Preoperatively, all patients were allowed to drink apple juice and water freely until 2 hours prior to surgery. Induction of anesthesia differed between ERAS and controls, as described below. All patients in both groups were monitored using bispectral index and an esophageal Doppler (33, 36). The esophageal Doppler probe was placed after induction of anesthesia, an optimal signal was obtained, indexed stroke volume (iSV) was maximized using 10 ml.kg⁻¹ 0.9% saline boluses, and the resulting value considered the reference. Intraoperative sufentanil boluses were administered to maintain mean arterial pressure and heart rate within 20% of the preoperative values. Any reduction in mean arterial pressure below 20% of the preoperative value and/or iSV below 15% of the reference value was treated with 10 ml.kg⁻¹ boluses of 0.9% saline then with 3 mg boluses of ephedrine. Maintenance of anesthesia was performed using sevoflurane in a 50% mixture of O₂/N₂O, and adjusted to maintain bispectral index values between 40 and 60. Tranexamic acid was administered to all patients intraoperatively - 10 mg.kg⁻¹ followed by a continuous infusion of 5 mg.kg⁻¹.h⁻¹ (33, 36). The transfusion target hemoglobin concentration was 8g.dl⁻¹ in all patients. All patients received antibiotic prophylaxis before induction of anesthesia (31). Patients in both groups received dexamethasone 0.15 mg.kg⁻¹ after induction, ondansetron 0.1 mg.kg⁻¹ at the end of anesthesia (19, 28), and 5 µg.kg⁻¹ intrathecal morphine (5), the latter performed by the surgeon during dissection. Body temperature was strictly maintained
between 36.5° and 37°C using a double warmer system on the lower and upper part of the body. Muscle relaxant was continuously administered during surgery and antagonized at the end of the surgery. Intraoperative maintenance fluid management consisted of Ringer’s Lactate administered according to the Holliday and Segar formula.

Postoperative analgesia was standardized according to a previously published protocol, and included morphine, paracetamol, NSAIDs and nefopam (16). Intravenous morphine was titrated in PACU, before connecting a Patient Controlled Analgesia (PCA) morphine pump that was continued on the ward (16). Pain was assessed using the numerical rating scale (NRS), and assessments were performed every 5 minutes during morphine titration, every 60 minutes during PCA use and every 4 hours after morphine discontinuation. In both groups, a dedicated pain team assessed patients at least daily with respect to the continuation and/or modification of morphine therapies. Non-opioid analgesia was also standardized and administered 30 minutes before the end of surgery or in PACU, consisting of intravenous or oral paracetamol 15 mg.kg⁻¹ 6 hourly, and intravenous Ketoprofen, 1 mg.kg⁻¹ 8 hourly or oral Ibuprofen 10 mg.kg⁻¹ 6 hourly, where there were no contra-indications. Nefopam was also administered to all patients 16 years or older in both groups at a dose of 0.25 mg.kg⁻¹ 6 hourly. Postoperative intravenous fluid administration consisted of a balanced crystalloid solution (B26®, APHP, Paris, France), at 2 ml.kg⁻¹.h⁻¹. Oral analgesics consisted of paracetamol 15 mg.kg⁻¹ 6 hourly, ibuprofen 10 mg.kg⁻¹ 6 hourly and oral morphine. Oral morphine was administered in both long acting (duration of action 12 hours: skenan LP® 0.5 mg.kg⁻¹.12h⁻¹) and short acting preparations (duration of action 4 hours: actiskenan® 0.1 mg.kg⁻¹ every 4 hours with a maximum daily dose of 1 mg.kg⁻¹) (16). Short acting morphine was administered before physiotherapy and in case of intense pain defined by a NRS ≥ 6. Finally, in both groups, PONV was prevented and treated (when required) using ondansetron 0.1 mg.kg⁻¹ 8 hourly.

In the control group, anesthetic induction was performed with intravenous propofol 5 mg.kg⁻¹, sufentanil 0.2 µg.kg⁻¹ and atracurium 0.5 mg.kg⁻¹. After orotracheal intubation, the patient was turned prone for surgery. Postoperatively, Morphine PCA dosing consisted of PCA boluses and a background infusion. Oral medication was introduced at postoperative day 2 and recovery of oral intakes and oral treatments, urinary catheter and surgical drain removal, mobilization and physiotherapy were at the discretion of the anesthesiologist, pediatrician and surgeon caring for patients.

In the ERAS group, specific education regarding the ERAS protocol was provided preoperatively, particularly emphasizing postoperative pain management and accelerated
recovery. Many ERAS protocol items were previously standard practice in the control group, including preoperative fasting, transfusion, the treatment of nausea and vomiting and temperature control. These items were formalized by the new standardized perioperative protocol of ERAS. Other protocol items differed between the two groups. Anesthesia induction was performed with propofol 5 mg.kg\(^{-1}\), ketamine 0.5 mg.kg\(^{-1}\) followed by a continuous infusion of 0.15 mg.kg\(^{-1}.h^{-1}\), and atracurium 0.5 mg.kg\(^{-1}\). After orotracheal intubation, the patient was placed in the prone position for surgery. Dexmedetomidine was then administered as an initial bolus of 0.4 mg.kg\(^{-1}\) over 10 minutes followed by an infusion of 0.04 µg.kg\(^{-1}.h^{-1}\). In the event of bradycardia below 50 bpm, dexmedetomidine was discontinued. Postoperatively, Morphine PCA dosing consisted of PCA boluses alone without background infusion. A cooling brace (GameReady® Company, Toulouse, France) was fitted to provide non-pharmacological analgesia over the first 24 hours (35). Oral analgesics were administered as soon as possible in the ERAS group and recovery of oral intakes and oral treatments, urinary catheter and surgical drain removal, mobilization and physiotherapy were clearly defined in the protocol.

**Surgical procedures**

All surgeries were performed by one of the three senior pediatric orthopedic spine surgeons. Posteromedial translation was the main technique used for posterior fusion, under continuous sensory and motor evoked spinal cord monitoring. Fusion levels were selected according to the same criteria during the entire study period. Surgical management and operating surgeons were unchanged through the two study periods.

**Outcomes**

The primary objective of the current study was to assess ERAS program efficacy as measured by hospital length of stay. Secondary outcomes were: ERAS items adherence, opioid consumption, opioids side effects (constipation, nausea and vomiting), pain intensity and postoperative wound infection within 30 days from surgery.

**Data collection and Statistical analysis**

Data collection consisted of demographic (age, weight), general (ASA status, preoperative administration of rEPO, intraoperative administration of tranexamic acid perioperative vasopressor use (without the doses), and surgical characteristics (number of levels fused,

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Thoracoplasty, intraoperative homologous and autologous transfusion. Other data consisted of a checklist of ERAS protocol components, namely: intraoperative antibioprophylaxis, perioperative gabapentin administration, multimodal analgesia administration (all non-opioid analgesics were collapsed as a single variable for the clarity of result), cooling brace use, opioid-sparing anesthesia, avoidance of back-up infusion of morphine during PCA, prevention and treatment of PONV, postoperative oral medication, time to oral liquids and solids, physiotherapy and time to removal of urinary catheters and surgical drains. Further ERAS data collected included the presence or absence of intraoperative hypothermia at any point intraoperatively (< 36.5°), the perioperative administration of non-opioid analgesics, opioid consumption from day 1 to 3, the pain scores (using the NRS) at rest and movement (maximum values for both conditions) reported from day 1 to 3, hospital length of stay and postoperative wound infection within 30 days from surgery.

Given the high probability of skewness in some continuous data such as pain scores, morphine consumption and HLOS non-parametric statistics were used. Continuous data were expressed as medians [range] and compared using the Mann-Whitney U non-parametric test. Differences were expressed as median difference and 95% confidence intervals. Discrete variables were expressed as numbers [percentage] and compared using the Chi2 test (or Fisher’s exact test).

In order to account for potential confounders, quantile regression analysis was performed (37). This was particularly relevant to factors that differed substantially between ERAS and control cohorts. Quantile regression is performed instead of linear regression where the conditions for linear regression are not met. The method of least squares (linear regression) estimates the conditional mean of the outcome across values of the predictor variables, whereas quantile regression estimates the conditional switch of outcome from one quantile to another according to the value of predictors. Guidelines usually recommend performing quantile regression on at least the 0.25, 0.5 and 0.75 quantiles for predicting the main outcome. However, given that the objective of this analysis was to study confounders, only the 0.5 quantile was explored.

Statistical analysis was performed using the SPSS 26 (IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp, USA). A p value of 0.05 was set as the limit of statistical significance.

Determination of the sample size

Length of hospitalization stay was chosen as the primary indicator of ERAS success. In a

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previous publication from our institution predating ERAS protocols, length of stay (SD) was found to be 5 (± 1) days. We hypothesized a 1 day reduction in length of stay with an alpha risk of 5% and a power of 90% post ERAS implementation. Required sample size was thus calculated as 21 patients per group (https://clincalc.com/stats/samplesize.aspx). Secondary outcomes were assessed in 200 patients based on the convenience of a sample of the annual case volume at our institution.

**Results**

Overall, 81 ERAS group patients and 82 controls were recruited. The recruitment flowchart is displayed in figure 1. Supplementary file 1 displays demographic and general patient data, along with anesthetic and surgical data. There were no significant differences between ERAS and control group patients.

Hospital length of stay was reduced in the ERAS group (figure 2: 4 [3; 16] days versus 7 [5; 19] days in the control group, p < 0.001). The estimated median difference in days of hospitalization was estimated to be -3 days [95% confidence interval: -2; -4].

Concerning ERAS items adherence, 80% of ERAS group patients correctly received preoperative carbohydrate loads, postoperative multimodal analgesia, gabapentin, opioid-sparing anesthesia, PCA alone without background morphine infusions, physiotherapy at day 1, and removal of surgical drains at day 1 (Supplemental file 1). Urinary catheters were removed by day 2 in 76.5% of patients (Supplemental file 2) and a cooling brace applied in 66.7%. Only one brace was available and was given to the first patient when two interventions were performed the same day. Some ERAS protocol items were already being performed during the control group period and did not differ between the two groups. These items include preoperative fluid intake, antibioprophylaxis, gabapentin, iSV directed fluid administration, maintenance of normothermia and the prevention and treatment of PONV (Supplemental file 2).

Total morphine consumption at day 1 was similar between the two groups but reduced in the ERAS group at days 2 and 3 (figure 3, Supplemental file 2). The estimated reduction in median morphine consumption was 25% and 35% at day 2 and 3, respectively. Pain intensity at rest and movement were also significantly reduced at days 2 and 3 (Supplemental file 2). The incidence of PONV did not differ between the two groups and the incidence of constipation reduced slightly but significantly in the ERAS group at day 3 (60 [73.2%] versus 46 [56.8%], 0.03 in the control and the ERAS cohorts, respectively). Lastly, the incidence of postoperative wound infection at 30 days did not differ significantly between the two groups.

Given the number of factors that might contribute to the decrease of length of stay, we
performed a quantile regression using all non-component ERAS factors exhibiting a significant difference between the ERAS and the control cohort. Those factors were: intraoperative sufentanil consumption, pain intensities (at rest and movement) at day 2 and 3, morphine consumption at day 2 and 3, and constipation (Supplemental file 2). Those factors together with the inclusion in the ERAS or the control cohorts were entered as cofactors in the quantile regression. Being in the control cohort and experiencing constipation at day 3 were the only two statistical predictors of increased HLOS (Table 1).

**Discussion**

The results of this study may be summarized as follows: the implementation of an ERAS protocol applied to surgical correction of adolescent idiopathic scoliosis resulted in a marked reduction in length of hospital stay.

Our major finding was a strongly significant reduction in length of hospital stay in the ERAS group. This result correlates with a previous study performed by Gotzinsky et al examining recovery following scoliosis surgery in children (2). This study recorded similar results, and the major ERAS protocol differences when compared with our cohort were the use of hydromorphone PCA instead of morphine PCA, the absence of an intraoperative OFA anesthesia protocol and the absence of the use of the cooling brace postoperatively.

Many hypotheses may be proposed to explain reduced HLOS in this context. The first and simplest is that the observed reduction of opioid consumption leads to shorter lengths of stay. Intravenous opiate PCAs with background infusions are commonly used following major surgery in children (5, 16). However, high doses of opioids are associated with many adverse effects, most commonly nausea, vomiting, constipation and sedation. These side effects impact negatively upon postoperative rehabilitation by delaying physiotherapy, oral intakes and urinary catheter removal, without any proven improvement in pain symptoms (16). This is highly supported by results of the quantile regression that found constipation as an independent predictor of length of stay. ERAS protocol items were introduced in 2016 aiming to reduce morphine consumption, and not previously part of standard protocols. They included the elimination of background morphine infusions, opioid-sparing and opioid-induced hyperalgesia reduction protocols (10, 15, 26), and a cooling brace. Gabapentin, an inhibitor of the voltage-dependent calcium channel, has been shown to reduce opioid consumption and improve postoperative recovery after spinal surgery in children; (2, 6, 27). This effect has been hypothesized to involve suppression of neuronal hyperexcitability in the afferent nociceptive pathway and to a lesser extent be a function of gabapentin’s anxiolytic
effect (38). Dexmedetomidine has also been found to reduce both postoperative pain and opioid consumption perioperatively (15, 26). Hypothetical mechanisms suggested as explanations for this finding include persistent postoperative analgesia and a reduction in opioid-induced hyperalgesia following intraoperative opioid-sparing (26). Despite the anti-hyperalgesic effect of ketamine being demonstrated in adults (39); results in children following scoliosis surgery do not favor its use (40-42). Any benefit from ketamine in our study is therefore likely due to intraoperative opioid-sparing effect. Furthermore, adherence to pre-existing multimodal analgesia protocols improve following the introduction of ERAS protocols (35). One can hypothesize that the sum of all the above led to reduced morphine consumption, reduced side effects, and accelerated rehabilitation. Indeed, morphine consumption was significantly reduced on days 2 and 3 as was constipation on day 3. Reduced opioid consumption has two other potential advantages: (a) it may result in reduced long term pain after surgery as a statistical relationship has been demonstrated between early opioid consumption and incidence of persistent pain following surgical correction of AIS (8, 9, 43, 44) and (b) it may reduce opioid misuse, particularly common in adolescents during the ongoing epidemic (11, 12).

A second element that may account for the observed reduction in hospital stay is the multidisciplinary implication of stakeholders in the ERAS project, including patients (45, 46). Recent research in organizational management emphasizes the importance of strategies improving multidisciplinary team collaboration around a common objective (22, 45, 46), such as teaming (47, 48). These key principles are of innovative and combined care practice. In practice, this means discussion between stakeholders, interdisciplinary boundary spinning and patient-centered activities (47, 48). Such strategies have been shown to increase both efficiency and performance. All these strategies are employed during ERAS implementation, favoring the emergence of a teaming effect toward a common objective (23). Moreover, the success of the protocol in reducing hospital stay probably acted as a virtuous circle for further motivation, a phenomenon recently described in motivation theory research (49-52). This is highly supported by the observed improvements in adherence to the administration of non-opioid analgesics following the ERAS program implementation without any concrete changes to protocols.

The third mechanism that might explain the reduction of length of hospital stay is patient involvement (21). Patients were educated about the ERAS protocol during both surgical and pre-anesthetic consultations. Patients with adolescent idiopathic scoliosis have been shown to suffer from anxiety and depression as a result of their condition (7). Such
symptoms may be exacerbated during the perioperative period, which in turn could result in increased opioid consumption, reduced motivation and reduced involvement in rehabilitation (e.g. physiotherapy) (7, 53). ERAS protocol education, perceived benefits and high postoperative motivation levels in both patients and caregivers may act synergically toward accelerated recovery. Pain intensity scoring was reduced in the ERAS group on days 2 and 3, both at rest and upon movement, despite less opioid consumption. Although the increased administration of non-opioid analgesics and the use of the cooling brace may have participated in reduced pain scores, one cannot exclude a beneficial effect of the ERAS protocol on patient psychological well-being. Psychological well-being has been shown to decrease postoperative pain and opioid consumption (53).

Some studies examining ERAS in children have been recently published, consistently demonstrating reduced length of hospitalization (2, 22). One previous study investigated an ERAS protocol in similar patients and demonstrated comparable length of stay reductions - despite shorter lengths of stay in their control group (2). Reduced length of hospital stay is a very significant result, given the efforts made to rationalize health care spending over the last couple of decades in public funded hospitals.

The current study suffers from one major limitation: it is an observational study comparing two historical cohorts. There is a possibility of bias with such non-controlled studies. However, we believe this methodology to be worthwhile as a first step, as there were no existing publications in this patient group at the time of implementation of ERAS for IAS in our institution, and furthermore, many publications examining ERAS programs in pediatric populations consist of observational evaluations (4, 54). The second limitation of this study is that a significant number of ERAS items were already being performed in the control population, as the formal implementation of our ERAS program was the result of some years of evolving protocols, published studies, clinical teaching sessions and meetings. Examples include preoperative fasting, time to postoperative oral intake antibioprophylaxis and temperature control. However, one important virtue of the formalized ERAS protocol was the improvement in implementation of these protocols.

In conclusion, the implementation of a specific ERAS program for surgical management of AIS resulted in reduced hospital length of stay, along with reductions in opioid use and constipation. These results should encourage others to implement formal ERAS programs in children, and to extend their use to other surgeries.
Legends of tables and figures

Figure 1: Patient Inclusion Flowchart

Figure 2: length of postoperative hospital stay. Data are expressed as median (line); 25% - 75% percentiles (boxes) and minimum – maximum (plots). ERAS: Enhanced Recovery After Surgery. ***: p < 0.001.

Figure 3: Morphine consumption during the first 3 postoperative days in ERAS patients and controls. ERAS: Enhanced Recovery After Surgery, PCA: patient-controlled analgesia, Oral: oral morphine, Total: total morphine consumption, NS: non-significant, **: p < 0.01, ***: p < 0.001. Data are expressed as median (line); 25% - 75% percentiles (boxes) and minimum – maximum (plots).

Supplemental file 1: Demographic, anesthesia and surgical data. Hb: hemoglobin; rEPO: recombinant erythropoietin.

Supplemental file 2: Primary, secondary outcomes and ERAS item adherence in control and ERAS group patients. Day 1 was defined as the calendar day at PACU admission.

Funding: Support was provided by our institution

Authors declare no conflict of interest.

The current study has been accepted for presentation at the annual meeting of the French Society of anesthesiology and intensive care on September 2019.

Authors’ contributions

Florence Julien-Marsoller: participated in study design, participating to quality of data assessment, data interpretation, revising the manuscript and approved the final version.

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Daphné Michelet: participated in study design, participating to quality of data assessment, data interpretation, revising the manuscript and approved the final version.

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Brice Ilharreborde: participated in study design, data interpretation, revising the manuscript and approved the final version.

Christopher BRASHER: participating to the questionnaire design, data interpretation, revising the manuscript and approved the final version.

Souhayl DAHMANI: participated in study design, participating to the questionnaire design, data analysis and interpretation, drafting and revising the manuscript and approved the final version.

References


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Annex 1: Enhanced Recovery After Surgery protocol. **Significant changes following the introduction of the protocol are displayed in bold.**

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<tr>
<th>Factor</th>
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<th>Standard Error of the regression coefficient</th>
<th>P value</th>
<th>95% confidence interval of the regression coefficient</th>
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<td>Morphine consumption (mg.kg(^{-1})) at day 2</td>
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<td>0.28</td>
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<td>-0.24 0.86</td>
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<td>0.13</td>
<td>0.27</td>
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<td>Pain intensity at movement (day 2)</td>
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<td>0.11</td>
<td>0.6</td>
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<td>0.11</td>
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<td>Absence of constipation (day 3)</td>
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<td>&lt; 0.0001</td>
<td>0.75 2.34</td>
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</tbody>
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Table 1: Quantile regression for the prediction of the quantile 0.5 (the median value) of the duration of length of hospital stay.
Length of stay (days)

Control

ERAS

***

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Title:
Enhanced recovery after surgical correction of adolescent idiopathic scoliosis

Date:
2020-08-29

Citation:

Persistent Link:
http://hdl.handle.net/11343/298012