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**Postsurgery analgesic and sedative drug use in a French neonatal intensive care unit: a
single-center retrospective cohort study**

Short title: Postsurgery analgesic and sedative drug use in a French NICU

A. Benahmed-Canat.¹, F. Plaisant¹, B. Riche, M. Rabilloud², G. Canat⁵, N. Paret³, O. Claris^{1,4}, B. Kassai³, K.A. Nguyen^{1,3*}

¹ Hospices civils de Lyon, Department of neonatology – Hopital femme mère enfant, Lyon,
69500 Bron, France

² Hospices civils de Lyon, Department of biostatistics – Lyon, 69500 Bron, France

³ Univ Lyon 1/UMR 5558/LBBE, Hospices civils de Lyon, Department of
pharmacotoxicology – Lyon, 69500 Bron France

⁴Univ Lyon 1/EA 4129

⁵Liberal general practitioner

***Corresponding author:**

Dr. Kim An Nguyen

Department of neonatology/Department of pharmacotoxicology

Hopital Femme-Mère Enfant

Hospices civils de Lyon

59, boulevard Pinel

69500 Bron

kim-an.nguyen@chu-lyon.fr

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Abbreviations:

GA: gestational age

SGA: small for GA

PDA: patent ductus arteriosus

ENT: ear nose throat

NICU: neonatal intensive care unit

What's known on this subject: Newborns admitted to a NICU are exposed to various sources of pain. The vast majority of analgesic and sedative molecules used in neonates are used off-label. The data relating to their efficacy and safety are insufficient.

What this study adds: The description of real use in a clinical setting of analgesic and sedative drugs and their adverse drug reactions in a neonatal intensive care unit (NICU) during the postsurgery phase.

ABSTRACT

Objective: To describe pain assessment, the pattern of analgesic and sedative drug use, and adverse drug reactions in a neonatal intensive care unit (NICU) during the postsurgery phase.

Method: Demographic characteristics, pain scores, and drug use were extracted and analyzed from electronic patient medical files for infants after surgery, admitted consecutively between January 2012 and June 2013.

Result: 168 infants were included. Acute (DAN score) and prolonged (EDIN score) pain assessment scores were used in 79% and 64% of infants, respectively, on the 1st day. This percentage decreased over the 7 days following surgery. The weekly average scores postsurgery were 2/15 (± 2.2) for the EDIN score and 1.6/10 (± 2.0) for the DAN score. The rates of pain control were 88% for the EDIN and 72% for the DAN. The most prescribed opiate drug was fentanyl (98 patients; 58%) with an average dose of 1.8 (± 0.6) $\mu\text{g}/\text{kg}/\text{h}$. Midazolam was used in 95 patients (56%), with an average dose of 35 (± 14) $\mu\text{g}/\text{kg}/\text{h}$. A bolus was administered in 7% (± 7.4) of the total dose for fentanyl and 8% (± 9.3) for midazolam. Similar doses were used in term and preterm neonates. Of 118 patients receiving fentanyl and/or midazolam, 40% presented urinary retention, 28% a weaning syndrome. Paracetamol (155 patients; 92%) and nalbuphine (55 patients; 33%) were the other medications most often prescribed.

Conclusion: The off-label use of fentanyl and midazolam was necessary to treat pain after surgery. Pain assessment should be conducted for all neonates in order to optimize their treatment. Research on analgesic and sedative medicine in vulnerable neonates seems necessary to standardize practices and reduce adverse drug reactions.

1. INTRODUCTION

Newborns admitted to a neonatal intensive care unit (NICU) are exposed to various sources of pain: acute pain during care or chronic pain stemming from the use of mechanical ventilation or from surgery conducted during the neonatal phase [1]. Since the 1980s, numerous preclinical and clinical studies have shown that the nervous system of preterm neonates was indeed able to conduct pain information after only 25 weeks of amenorrhea [2]. Studies showed that neonates are actually more sensitive to pain than older infants [3]. Their immature nervous system, far from protecting them from pain, actually makes them more vulnerable to it, with even greater sensitivity in the case of preterm neonates. Excessive stimulation of the nociceptive pathways during the high-plasticity developmental phase of the nervous system could be the source of functional alterations, with modified sensitivity to pain lasting far into childhood, as well as an impact on neurobehavioral development [4].

Although addressing pain in neonates has today become a priority, most clinicians are faced with several challenges. The first point regards assessment of pain. Pain assessment scales, established on the basis of physiological and behavioral responses, prove extremely useful and allow regular assessments, but since no gold standard has been set, a strong variability can be noted in the use of these scales in different neonatal care units. The scales also have their own limitations since several factors can influence the response to pain: gestational age, postnatal age, neurobehavioral state, previous pain experiences [5], use of sedatives or curarization, or existing neurological damage.

Some countries have developed guidelines to standardize the way pain in neonates is addressed [6-8]. These guidelines insist upon a step-by-step approach to pain and highlight the importance of limiting painful procedures. They also underline the importance of non-drug techniques. Nevertheless, the use of analgesic and sedative drugs seems unavoidable for acute pain or in situations such as mechanical ventilation or surgery conducted during the

neonatal phase. However, the vast majority of analgesic and sedative molecules used in neonates are used off-label, the second challenge faced by clinicians. Most drugs used in neonates are the same as those used in adults and stem from adult intensive care practices. Consequently, their use is based on an extrapolation of studies conducted in adult patients. It is known, however, that the pharmacokinetics and pharmacodynamics of neonates clearly differ from those of adults and older infants, even more so where preterm neonates are concerned [9]. Like many drugs, for several reasons, analgesic and sedative drugs are rarely studied in the treatment of term and preterm neonates, and the data relating to their efficiency and safety are insufficient [10]. The side effects of hypnotics and morphine derivatives are relatively frequent, in particular in preterm neonates [11].

In this context, the present study aimed to describe pain assessment, the pattern of analgesic and sedative drug use, and their adverse drug reactions in a NICU during the postsurgery phase.

2. METHODOLOGY

2.1 Study design

This single-center study was a retrospective observational study that collected data on postoperative pain management (pain assessment and pain treatment) in neonates admitted to the participating NICU in a French university hospital who had undergone surgery. All infants undergoing surgery, including preterm and term neonates younger than 28 days were included consecutively when admitted to the study NICU during the 18 months between January 2012 and June 2013. Our 52-bed NICU receives 750–800 patients per year with 12% of infants needing surgery.

2.2 Data extraction

Data were extracted anonymously from the electronic patient medical files (IntelliSpace Critical Care and anesthesia, ICCA, Philips Healthcare, France). This study was approved by the local ethics committee on 6 June 2011 (CPP sud est II, no C.A.L 2011-15). The data collected included gestational age (weeks) at birth (in France, gestational age is calculated in weeks of amenorrhea from the last day of menorrhoea), birth weight (grams), intrauterine growth restriction (IUGR) according to the AUDIPOG curve, http://www.audipog.net/courbes_morpho.php?langue=en), type of surgery, age and weight at surgery, analgesic and sedative drugs administered, dose and duration of use (days), length of hospital stay (days), duration of ventilation (days), pain scores, and adverse drug reactions. The two pain-monitoring scores used systematically as a local protocol for all infants during the 1st week in the unit were the EDIN (Échelle Douleur Inconfort Nouveau-né) [12] and DAN (Douleur Aiguë du Nouveau-né) [13] scores. The nurses were trained and were used to this protocol. They assessed pain at least every 3 h (as prescribed by doctors) or more frequently if necessary. Only doctors could modify analgesic and sedative drug dosage or order the bolus. We did not find any consensus on the pain-free score for the two scales, so we defined “no pain” for an EDIN score < 5/15 and a DAN score < 3/10, which is accepted in the local protocol and according to the studies examining these scales [12,13], which allowed us to calculate the no-pain rate (proportion of scores indicating no pain).

Term at date of surgery (< 32 weeks, [32–35], [35–37], ≥ 37 weeks) and weight at the date of surgery (< 1500 g, [1500–2000], [2000–2500], ≥ 2500 g) were categorized a priori. A more detailed analysis of the pain scores, analgesic and sedative drugs, and doses administered was conducted over the first 7 days following surgery (or until discharge/death). The data analyzed included the precise doses (µg/kg/h) of analgesic and sedative drugs used in continuous treatment (fentanyl, morphine, sufentanil, midazolam, ketamine) as well as all

dose modifications (date and time) and the date, time, and dose of boluses administered. Nurses administer boluses of drugs (midazolam or opioid) before procedures (endotracheal suctioning for example) or when the patient is presenting signs of pain despite continuous analgesia. The date and time of administration for analgesic and sedative drugs in discontinuous treatment (acetaminophen, nalbuphine, morphine administered orally) were also collected, only with agreement and medical prescription. The doses used ($\mu\text{g}/\text{kg}/\text{h}$) were analyzed for midazolam and fentanyl in continuous treatment: the starting dose (initial dose), maximum dose, average dose, and cumulative dose in continuous treatment in $\mu\text{g}/\text{kg}$ over the 7-day period.

2.3 Method to assess adverse drug reactions

We used a chart review method to detect adverse drug reactions, focusing on frequent adverse drug reactions such as acute urinary retention and withdrawal syndrome. All adverse events were transmitted anonymously by the study investigators to the regional pharmacovigilance center, which evaluated them independently. Withdrawal syndrome was only retained if mentioned in the patient file or when the Finnegan withdrawal score was ever ≥ 11 , or ≥ 8 in three consecutive assessments. These criteria were inspired and adapted from the study reported by Zimmermann et al. [14]. In our local practice, the Finnegan score was indicated every 3 or 4 h by doctors when withdrawal syndrome was clinically suspected in infants after the end of analgesic and sedative treatment.

2.4 Statistical analyses

A descriptive analysis of the data and pain control was also conducted using R software (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>). Demographic and clinical characteristics were summarized for all subjects, using counts and

percentages for categorical data, and the mean \pm standard deviation (SD) or median (range [IQR]).

Using a logistic regression model, we studied the probability of no pain and the influence of explanatory factors such as term at the date of surgery, weight at the date of surgery, or the type of surgery). The results of regression analyses are presented as probabilities (%) with two-sided 95% confidence intervals (CIs).

3. RESULTS

3.1. General characteristics of patients and surgeries

Between January 2012 and June 2013, 178 out of 1063 newborns who were admitted to the study NICU underwent surgery. Among these, ten patients were excluded because of missing data. A total of 168 patients were included in the study. Slightly less than half (46.4%) were term patients (gestational age at birth $>$ 37 weeks). Nearly one-third (30.4%) of the neonates included were small for their gestational age (SGA). The characteristics of patients and type of surgery are presented in Table 1. The median [IQR] duration of the hospital stay was 27.2 [8.3–62.4] days, including a median [IQR] duration of 8.0 [3.3–20.6] days in the NICU.

3.2. Description of pain monitoring

Over the first 7 days following surgery, the median [IQR] EDIN score per patient per day was 2 [0–11] and the median [IQR] DAN score per patient per day was 1 [0–15]. On day 1, 2, 3 the postsurgery median [IQR] EDIN score per patient per day was 2 [0–9], 5 [0–8], and 5 [0–11], respectively. On the 1st day after surgery, there was no acute (DAN score) pain assessment in 21% of the patients and no prolonged (EDIN score) pain assessment in 36% of the patients. This percentage increased over the 7 days following surgery (see Figure 1). The weekly median [IQR] postsurgery score was 2 [0–3] for the EDIN and 1 [0–3] for the DAN.

The no-pain rate was 88% for the EDIN scores and 72% for the DAN scores over the first 7 days after surgery.

The probability for no pain was high: 91.5% [95% CI, 90.1; 93.4%] based on the EDIN scores (Figure 1) and 76.3% [95%CI: 72.6; 79.7%] based on the DAN scores.

3.3. Analgesic and sedative drugs used between the 1st and 7th day postsurgery

The analgesic and sedative drugs used were: acetaminophen (paracetamol), midazolam, fentanyl, nalbuphine, morphine, sufentanil, and ketamine (Figure 2); a mean 2.6 (\pm 1.3) different drugs were received per patient per surgery. Nalbuphine was not used concomitantly to opioids. Fentanyl was the opioid drug prescribed to the greatest number of patients (98 patients, 58%). The mean dose was 1.8 μ g/kg/h (\pm 0.6). Midazolam was used in 95 patients (56%) at a mean dose of 35 μ g/kg/h (\pm 14).

3.4. Adverse drug reactions

Considering all surgeries ($n=213$), 49 cases (23%) of acute urinary retention and 30 (14%) withdrawal syndromes were identified. One patient presented with another declared adverse drug reaction (bradycardia following a dose of nalbuphine).

Restricting the analysis to patients who received either midazolam, morphine, fentanyl, or sufentanil during their hospital stay ($n=118$), the frequency of adverse drug reactions was as follows: 43 (39.8%) cases of acute urinary retention, 41 after the first surgery; 28 (23.7%) cases of withdrawal syndrome, 22 after the first surgery. A total of 63 (53.4%) surgeries were followed by at least one adverse drug reaction. Cases of acute urinary retention occurred a mean 1.6 (\pm 2.7) days after surgery, after 1.5 (\pm 2.7) days of midazolam use, and after 1.7 (\pm 2.8) days of use for opiates. Withdrawal syndromes occurred a mean 11.3 (\pm 13.1) days after surgery, after 10 (\pm 9.1) days of midazolam use, and after 9.8 (\pm 9.2) days of use for opiates.

4. DISCUSSION

The present study describes postoperative pain assessment and medical treatment and their adverse drug reactions in a NICU. The results showed that pain scores were low regardless of gestational age, weight, and type of surgery, but they were sometimes missing. Indeed, there were no acute (DAN score) and prolonged (EDIN score) pain assessments in 21% and 36% of infants, respectively, on the 1st day, and this percentage increased with the postoperative time. This could be a prescription omission or an omission on the part of the nurses in charge. One hypothesis is that the children concerned did not show signs of pain due to the prolonged effect of anesthetic drugs and that the nurses did not find it useful to report a score of 0. This result is close to the percentage observed in the multicenter observational study conducted by Taylor et al. [15] in 2006 in ten NICUs, with 250 newborns: pain assessment by nurses was documented for 88% of the patients. Pain assessment using adequate scores should be systematically conducted in order to orientate the use of analgesics. In the present study, two validated pain scales, the EDIN and the DAN were used. However, there is no gold standard pain assessment scale. In the multicenter study published by Taylor et al. [15], participating hospitals used seven different numeric pain scales, which shows the wide variability of use.

Many validated pain scales exist, based on the physiological and behavioral response to pain. Some are tailored for acute pain (NFCS, Neonatal Facing Coding System [16], NIPS, Neonatal Infant Pain Scale [17] and the DAN); other scales are tailored for chronic and postoperative pain such as the EDIN and the PIPP (Premature Infant Pain Profile) [18], and some are adapted for premature neonates. The two pain scales used are based on behavioral responses, which are difficult to assess in sedated, ventilated neonates. Furthermore, these scales could not distinguish overly sedated patients. Both the EDIN and DAN scores remained low over the 7 days after surgery regardless of weight, term, and type of surgery.

These low pain scores could suggest excessive doses of the analgesic and sedative drugs, which could in turn trigger adverse effects. The low pain scores also suggest that neither the EDIN or the DAN was appropriate to assess infants after surgery. A COMFORT scale would be more appropriate for ventilated and/or postoperative infants [19].

The second part of the study was the description of the analgesic and sedative drugs used. Most drugs were used off-label in terms of age (fentanyl, midazolam, nalbuphine, sufentanil, ketamine, and morphine). There is a lack of robust evidence on the efficacy, safety, and dosage of most sedative and analgesic drugs used in neonates; their pharmacokinetics and pharmacodynamics remain underinvestigated. Randomized controlled studies are rare, and the recommendations for dosage suggest wide ranges [20].

Approximately 70% of 119 patients received an intravenous opioid, which is comparable to the number observed in the Taylor multicenter study (84% in major surgeries, 60% in minor surgeries). According to the local protocol, fentanyl (98 patients) was the most frequently used opiate in the study unit. Fentanyl may be used as a bolus and/or as an intermittent dosing of 0.5–2.0 µg/kg or as a continuous infusion of 0.5–2.0 µg/kg/h [21]. In the present study, the average dose of fentanyl was 1.8 (±0.6) µg/kg/h. This dosage was very close to the maximum dose recommended. This high dose might explain the low pain scores in the study because the patients may have been oversedated. Fentanyl is almost 100 times more potent than morphine. Although morphine remains the most widely studied opiate for use in neonates and has shown a lower risk of tachyphylaxis [22, 23], morphine should be used with caution in preterm neonates because of the adverse neurodevelopment effects shown by some studies [24, 25]. Due to the uncertainty of their long-term side effects on neurodevelopment in newborns, clinicians should pay more attention to the minimum effective dose when using opioid drugs.

Over the 7-day period after surgery, 95 patients out of 168 (57%) received midazolam as a continuous treatment. In Taylor et al.'s study, benzodiazepines were used for 24% of

major surgeries and 11% of minor surgeries, a much lower rate. Midazolam is a sedative and not an analgesic drug. Its efficacy on sedation scores has been proven in randomized studies. It eases ventilation in neonates and can also reduce pain scores for certain interventions. A systematic review by the Cochrane Collaboration Group, updated in 2012 [26], identified only three randomized controlled studies that investigated the use of sedative drugs in neonates (< 28 days) in NICUs in which midazolam was used continuously. The authors concluded that the data were insufficient on the use of midazolam as a sedative in neonates in NICUs. In the NOPAIN study [27], a link was found between midazolam and intraventricular hemorrhage. To this day, the impact of midazolam on long-term neurological development is still a cause of concern. In severe preterm or very-low-birth-weight neonates, the elimination of the drug is highly delayed compared to term neonates, which leads to a build-up of the drug parallel to continuous infusions [28]. Considering the concerns in terms of adverse effects, the use of a minimum efficient dose, adapted to the patient's term and gestational age, is crucial. But these results need to be weighed against the negative effect of pain in the neonatal brain [4].

An important observation in this study is that the average doses used in very preterm or low-weight neonates are close to those used in term neonates (excluding the extreme groups of neonates under 28 weeks and neonates under 1000 g, in whom the doses appear high, although these groups only comprised two and three patients, respectively). This practice may expose preterm patients to a higher risk of overdose and to an increase in adverse drug reactions. This absence of variation between average doses in different term and weight situations is startling, since elimination of both fentanyl and midazolam is much slower in lighter and preterm neonates [29, 30]. An insufficient assessment of pain in very premature neonates due to unsuitable pain scales could be hypothesized to explain this. An insufficient assessment could lead to inadequate doses. Another hypothesis could be a need for a higher plasma level of drugs to reach efficacy in premature neonates. This could be due to the

maturational stage of pain tracts and neurotransmitters in premature newborns, which increase pain sensitivity. We also observed that the dose administered as a bolus increases as term and weight increase. To the best of our knowledge, the efficacy and safety of bolus dosing have not been evaluated in neonates.

Adverse drug reactions are frequent in the study population. We focus on two common adverse drug reactions due to opiates and sedatives in neonates: acute urinary retention and withdrawal syndrome. In patients treated with opiates and/or midazolam in continuous treatment, more than half of the patients presented at least one of these adverse drug reactions. These are not the most severe potential secondary effects associated with these drugs, however: opiates and sedatives can also trigger more serious adverse drug reactions (hypotension, respiratory effect, bronchospasm, digestive effect, etc.). Due to the particular status of infants in the postsurgery phase, it was too difficult to establish the imputability of such events related to analgesic and sedative drugs.

5. Conclusion

Based on these findings, there is a need to fine-tune these drug uses with better pain assessment and deeper knowledge of these drugs, to define the minimum effective dose. Pain should be assessed for each neonate to optimize treatment. But many available pain scales are subjectively based on behavioral and physical changes. Other objective and continuous methods to assess pain in NICUs are needed. There is a lack of evidence regarding the efficacy, safety, and dosage of most sedative and analgesic drugs currently used in NICUs. Further research on analgesic and sedative medicine in vulnerable neonates is necessary to standardize practices and reduce adverse drug reactions. Development of new drugs may also be encouraged.

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Table 1: Characteristics of patients at first surgery ($n=168$)

	Study population $n = 168$
Mean GA at birth, weeks \pm SD	35.1 \pm 4.6
Mean birth weight, g \pm SD	2337.1 \pm 1006.0
Small for GA, n (%)	51 (30.4)
Sex ratio, M/F	100 / 68
Median age at surgery, days [IQR]	4 [0-142]
Mean GA at surgery, weeks \pm SD	38.1 \pm 3.3
Mean number of surgeries per patient, $n \pm$ SD	1.3 \pm 0.7
Number of surgeries per patient, n (%)	

1	136 (81.0)
2	23 (13.7)
3	6 (3.6)
4	2 (1.2)
5	1 (0.6)
Surgery, <i>n</i> (%)	
Abdominal-pelvic / urogenital	69 (41.1)
Thoracic	20 (11.9)
Head and neck	19 (11.3)
Orthopaedic	3 (1.8)
Inguinal and ovarian hernia	27 (16.0)
Light urogenital	9 (5.3)
Biopsies	8 (4.8)
Anal plastic	6 (3.6)
ENT endoscopies	6 (3.6)
Cutaneous	1 (0.6)
Ventilation before surgery, <i>n</i> (%)	
Spontaneous	141 (84.4)
Assisted	26 (15.6)
Missing data	1
Duration of ventilator support for infants with spontaneous ventilation before surgery, days, median [IQR]	0.5 [0–4]
Mean duration of hospital stay, days, median [IQR]	27.2 [8.3–62.4]
Mean duration of NICU stay, days, median [IQR]	8.0 [3.3–20.6]

GA, gestational age; SGA, small for GA; NICU, neonatal intensive care unit

Figures

Figure 1: Pain assessment with EDIN score^a day 1–7 after surgery

^a Pain scores: EDIN score, Échelle Douleur et Inconfort Nouveau-né

^c Day 1–7, postoperative days. Day 1 is the day of surgery

Figure 2: Sedative and analgesic molecules used during the first 7 days after surgery (Day 1 to day 7 postsurgery. Day 1 is the day of the surgery)

IV, intravenous; IR, intrarectal; PO, per os

Figure 1:

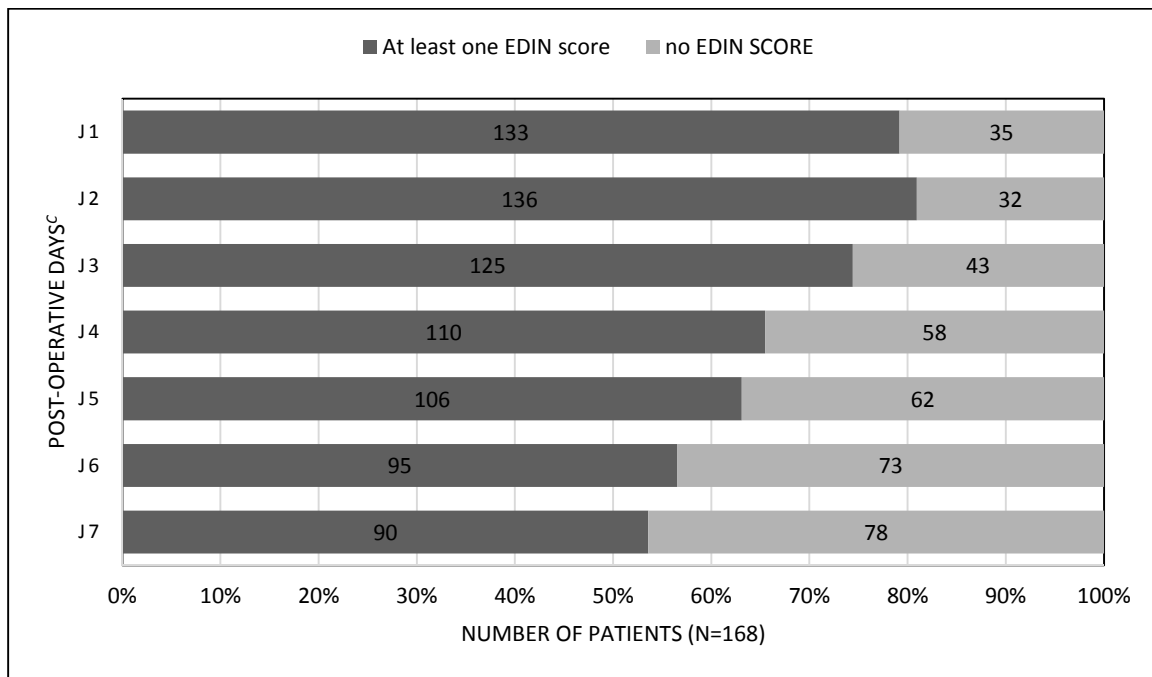


Figure 2:

