

# Neuroblastoma in Children: Intraoperative Goal Directed Therapy, Intraoperative And Postoperative Outcomes

Claudine Kumba (✉ [claudine.kumba@gmail.com](mailto:claudine.kumba@gmail.com))

Hôpital Universitaire Necker Enfants Malades, Assistance Publique Hôpitaux de Paris, APHP, Université de Paris

---

## Short Report

**Keywords:** Neuroblastoma, Children, Intraoperative Goal Directed Therapies, Postoperative Outcomes

**Posted Date:** August 6th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-785499/v2>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

**Background:** Neuroblastoma is the most common tumor in children. Anesthetic management can be challenging due to the localization and catecholamine-secreting characteristics of the tumor. We undertook a secondary analysis in a previous study to describe patients who underwent neuroblastoma resection.

**Objective:** To describe intraoperative and postoperative outcomes in patients who underwent neuroblastoma resection and to propose optimal intraoperative management for postoperative outcome improvement.

**Methods:** This was a secondary analysis of children who underwent neuroblastoma resection in the initial retrospective study.

**Results:** There were 16 patients with a mean age of  $39.3 \pm 22.1$  months. Seven (43.8%) patients presented with intraoperative or postoperative complications. One (6.3%) patient had intraoperative broncholarynospasm and difficult intubation. Two (12.5%) patients had intraoperative hemorrhagic shock. One patient (6.3%) had postoperative renal failure. Two patients (12.5%) had postoperative respiratory failure, and 3 (18.8%) patients had postoperative cardiocirculatory failure. One (6.3%) had postoperative pulmonary sepsis and septicemia. Thirteen (81.3%) patients were intraoperatively transfused. There was no in-hospital mortality.

**Conclusion:** Neuroblastoma surgery can be a challenging situation where cardiovascular instability, high blood loss and transfusion requirements can be encountered. Consequently, preoperative preparation and optimal intraoperative management with validated means in children are necessary for a better postoperative outcome in this surgical setting.

## Introduction

Neuroblastoma is the most common tumor in children, with an incidence of 10.2 per million children under 15 years old, and is responsible for 13-15% of deaths due to cancer in children (1,2,3,4). Long-term prognosis depends on the characteristics of the tumor, with five-year survival in low-risk and high-risk neuroblastoma varying from 90-95% to 40-50%, respectively (2,5). Surgical complications after surgery depend on the localization of the tumor and vary, including chyloabdomen, chylothorax, Horner syndrome, pneumothorax, injury of the renal blood vessels, and injury of the inferior vena cava (6,7).

Neuroblastoma can present different localizations as an abdominal mass from medulla adrenergic cells in 35% of cases, as spinal paraspinal ganglia in 35% of cases, as posterior mediastinal masses in 20% of cases, and as pelvis and neck masses in 5% of cases (1). Therapeutic management of these tumors is multidisciplinary and can include surgery, chemotherapy, autologous stem cell transplant, radiotherapy, and immunotherapy depending on the characteristics of the tumor (1).

Anesthetic management of neuroblastoma surgery can be challenging due to catecholamine secreting characteristics, such as a mediastinal presentation, which can cause cardiocirculatory collapse at the induction of anesthesia and increased blood loss if the tumor is close to great vessels (6,7,8,9,10). This emphasizes the importance of preoperative preparation of these tumors for optimal intraoperative management.

In a previously published retrospective study in 594 patients that reported predictors of intraoperative and postoperative outcomes, there were patients who underwent neuroblastoma surgery (11).

We aimed to describe intraoperative and postoperative outcomes in neuroblastoma surgical patients included in the initial study as a secondary analysis (11). The secondary objective of this analysis was to propose intraoperative management for optimal postoperative outcome in this surgical setting where intraoperative cardiocirculatory instability, blood loss and fluid therapy requirements can be high.

## Methods And Materials

A secondary analysis of patients who underwent neuroblastoma surgery was included in the initial study (11).

The study was approved by the Ethics Committee of Necker Enfants Malades University Hospital under registration number 2017-CK-5-R1 on 21 March 2017.

Patients were retrospectively included from 1 January 2014 to 17 May 2017.

The inclusion criteria were patients who underwent neuroblastoma resection aged less than 18 years old and were included in the initial study.

The exclusion criteria were patients who did not undergo neuroblastoma surgery and aged more than 18 years old included in the initial study.

Statistics were analyzed with XLSTAT 2020.4.1. software. Continuous variables were expressed as medians with ranges or means with standard deviations. Categorical variables were described in proportions.

In our hospital, patients who are scheduled for catecholamine-secreting neuroblastoma surgery were managed according to a defined protocol described here.

Preoperatively, patients had prazosin at 0.015 mg/kg to 0.5 mg/kg/day administered three times orally.

Labetalol could be administered at 5 to 15 mg/kg/day (as a maximum dose of 5 mg x3/day) in 2-3 times orally or 0.5-1 mg/kg/h as an intravenous (IV) infusion in cases of secondary tachycardia with alpha-blocking agents.

Acetabutolol could be administered at 5-15 mg/kg/day twice in cases of secondary tachycardia with alpha-blocking agents or refractory hypertension.

Nicardipine could be administered preoperatively as an intravenous (IV) infusion at 0.5-2 µg/kg/minute for refractory hypertension.

Surgery was scheduled at least 14 days after antihypertensive therapy was started and controlled. All patients had a preoperative echocardiography, a complete blood cell count, coagulation tests depending on the patient's status, blood urea nitrogen, creatinine plasmatic levels, complete plasmatic electrolyte levels, available cross-match and packed red blood cells in case of intraoperative transfusion.

Before induction of anesthesia, an intravenous peripheral line was available.

Induction of anesthesia was performed in a smooth manner with sevoflurane in a mixture of air and oxygen and intravenous sufentanil at a 0.2 µg/kg bolus. Airway was secured with endotracheal intubation. Maintenance of anesthesia was performed with sevoflurane in air-oxygen, IV sufentanil at 0.05µg/kg bolus, muscle relaxation for surgical reasons could be performed with IV cisatracurium at 0.15 mg/kg or rocuronium at 0.6 mg/kg bolus.

Antibiotic therapy was performed with cefazolin 50 mg/kg intravenously.

Two large-bore peripheral intravenous lines were inserted, and an indwelling bladder catheter, nasogastric tubing, a central core temperature probe, and a muscle relaxation monitoring device were inserted. All patients had a rapid fluid infusion pump and a fluid warming device available.

After the induction of anesthesia, an arterial catheter and a central venous line were inserted. According to the surgical technical approach (laparotomy versus laparoscopy), an epidural catheter or paravertebral catheter was inserted for intraoperative and postoperative analgesia. Analgesia with an epidural catheter or paravertebral catheter was performed with levobupivacaine 0.125% or 0.0625% at 0.2-0.3 ml/kg/h according to the age of the patient.

Intraoperatively, intravenous urapidil was administered at 2 mg/kg/h as a starting infusion dose and at 0.8 mg/kg/h as a maintenance infusion dose to manage hypertension.

Intravenous esmolol in cases of tachycardia or refractory hypertension could be started as an infusion at 25-200 µg/kg/h.

Intravenous labetamol as an infusion at 0.25-2 mg/kg/h could be administered as an alternative to urapidil or esmolol.

Intraoperative fluid therapy with crystalloids (Ringer Lactate® or chloride sodium 0.9%) or with colloids (plasmion® or voluven ®) was managed with the aims of avoiding catecholamine-induced hypovolemia, vasodilation due to antihypertensive medications and hypotension after tumor resection.

Glycemia was monitored, and 5% glucose-containing crystalloids were administered to avoid hypoglycemia after tumor resection.

Postoperative analgesia was performed with IV acetaminophen 15 mg/kg/6h, epidural or paravertebral catheter with levobupivacaine 0.125% or 0.0625% at 0.1-0.2 ml/kg/h, IV nalbuphine at 0.2 mg/kg/6h or IV morphine as patient controlled analgesia bolus if necessary.

Patients were extubated in the operating room and transferred to the postinterventional care unit and afterwards to the pediatric intensive care unit for surveillance.

## Results

Table 1 illustrates general characteristics

There were 16 patients with a mean age of  $39.3 \pm 22.1$  months and a median weight of 13[5.2-22] kilograms. There were one (6.3%), three (18.8%), and twelve (75%) American Society of Anesthesiologists (ASA) grade 1, 2 and 3 patients, respectively. All patients had elective surgery. There were no reoperations. Seven (43.8%) patients presented with intraoperative or postoperative complications. One (6.3%) patient had intraoperative bronchospasm and difficult intubation. Two (12.5%) patients had intraoperative hemorrhagic shock. One patient (6.3%) had postoperative renal failure. Two patients (12.5%) had postoperative respiratory failure, and 3 (18.8%) patients had postoperative cardiocirculatory failure. One (6.3%) had postoperative pulmonary sepsis and septicemia. Thirteen (81.3%) patients were intraoperatively transfused with packed red blood cells (PRBCs) and/or fresh frozen plasma (FFP) and/or concentrated platelet units (CUPs). There was no in-hospital mortality.

The mean preoperative and postoperative hemoglobin levels were  $10.1 \pm 0.9$  g/dL and  $11.1 \pm 2.2$  g/dL, respectively. The median crystalloid and colloid volumes were 1300 [100-2900] ml and 305 [60-1000] ml, respectively. The median length of intensive care unit stay (LOSICU) was 7[0-16] days. The median length of hospital stay in the conventional ward (LOS) was 8.5[1-17] days. The median total length of hospital stay (TLOS=LOSICU+LOS) was 15[3-33] days. The median length of mechanical ventilation (LMV) was 0.5[0-5] days.

Table 2 illustrates co-morbidities

The most common comorbidity was cancer in eight (50%) patients, followed by chronic renal failure in one (6.3%) patient.

## Discussion

Intraoperative neuroblastoma surgery can be a challenging situation because of the possible hemodynamic instability that can be observed in catecholamine-secreting tumors, due to the anatomic

position of the tumor, which can be near great vessels with possible increased blood loss and transfusion requirements during surgery. Intraoperative fluid and hemodynamic therapy guided with validated tools in children is mandatory in this surgical setting. Esophageal Doppler probes and transthoracic echocardiography to assess fluid responsiveness with aortic peak flow velocity are validated tools in children and should be integrated in intraoperative patient management (12,13,14,15,16,17) in this setting. Non-optimal regional renal oxygen saturation, cerebral oxygen saturation (as assessed with near infrared spectroscopy NIRS), lactate levels and mixed central venous oxygen saturation values have been correlated with adverse postoperative outcomes in terms of morbidity and mortality in children; thus, these parameters should be part of the monitoring in neuroblastoma surgery (18).

Neuroblastoma resection is a potential hemorrhagic surgery, as illustrated by the results of this study, where the transfusion rate is high. Transfusion goal-directed therapy with point-of-care viscoelastic assays needs to be part of patient blood management in this surgery to optimize blood product administration and postoperative outcome in terms of morbidity and LOS (19,20,21,22). As described previously in other potential hemorrhagic surgeries, point-of-care viscoelastic methods serve as a guide to transfuse the right product at that right time with results available within ten minutes, which is faster than conventional coagulation tests.

Intraoperative goal-directed therapies with validated tools need to be part of patient management in major surgery in children for intraoperative and postoperative optimization (27,28,29,30,31,32).

## Conclusion

Neuroblastoma surgery can be a challenging situation where cardiovascular instability, high blood loss and transfusion requirements can be encountered. Consequently, preoperative preparation and optimal intraoperative management with validated means in children are necessary for a better postoperative outcome.

## Declarations

**Conflicts of Interest:** The author declared no conflicts of interest.

**Funding:** None

**Author contributions:** Claudine Kumba conceptualized and designed the study and drafted the initial manuscript. She designed the data collection instruments, collected data, carried out

initial and final analyses.

**Ethics Approval:** This study received approval from the Ethics Committee of Necker on 21 March 2017 under registration number 2017-CK-5-R1 and waived patient consent.

## References

1) Hallett A, Traunecker. A Review and Update on Neuroblastoma. *Paediatrics and Child Health* 2011;22:33.

2) Colon NC, Chung DH. Neuroblastoma. *Adv Pediatr.* 2011 ; 58(1): 297–311.  
doi:10.1016/j.yapd.2011.03.011.

3) Gomez-Rios MA, Nuno FC, Barreto-Calvo P. Anesthetic Management of An Infant With Giant Abdominal Neuroblastoma. *Rev Bras Anesthesiol* 2017; 67 (2):210-213.

4) Louis CU, Shohet JM. Neuroblastoma: Molecular Pathogenesis and Therapy. *Annu Rev Med* 2015; 66:49-63. doi:10.1146/annurev-med-011514-023121.

5) Schengrund CL. Gangliosides and Neuroblastomas. *Int. J. Mol. Sci.* **2020**, *21*, 5313; doi:10.3390/ijms21155313.

6) Liu T, Lv Z, Xu W, Liu J, Sheng Q. Role of Image-defined risk factors in predicting surgical complications of localized neuroblastoma. *Pediatric Surgery International* 2020 ; <https://doi.org/10.1007/s00383-020-04731-y>.

7) Malek M, Mollen KP, Kane TD, Shah SR, Irwin C. Thoracic neuroblastoma: a retrospective review of our institutional experience with comparison of the thoracoscopic and open approaches to resection. *Journal of Pediatric Surgery* 2010 ; 45 :1622–1626.

- 8) Cheung SLW, Lerman Jerrold. Mediastinal Masses and Anesthesia in Children. *Anesthesiology Clinics Of North America* 1998;16 (4):893-910.
- 9) Kumba C (2019) Pheochromocytoma, Paraganglioma, Neuroblastoma, Catecholamine Secreting Tumor Perioperative and Anesthetic Management in Children. *Int J Pediatr Neonat Care* 5: 156. doi: <https://doi.org/10.15344/2455-2364/2019/156>.
- 10) Stricker PA, Gurnaney HG, Litman RS. Anesthetic Management of Children With an Anterior Mediastinal Mass. *Journal of Clinical Anesthesia* 2010 ; 22 : 159–163.
- 11) Kumba C, Cresci F, Picard C et al (2017) Transfusion and Morbi-Mortality Factors: An Observational Descriptive Retrospective Pediatric Cohort Study. *J Anesth Crit Care Open Access* 8(4): 00315. DOI :10.15406/jaccoa.2017.08.00315.
- 12) Tibby SM, Durward A, Murdoch IA. Are transoesophageal Doppler parameters a reliable guide to paediatric haemodynamic status and fluid management? *Intensive Care Med* 2001;27 (1):201-5.
- 13)Murdoch IA, Marsh MK, Tibby SM, McLuckie A. Continuous Haemodynamic Monitoring in Children: Use of Transoesophageal Doppler. *Acta Paediatr* 1995; 84(7):761-4.
- 14)Weber T, Wagner T, Neumann K, Deusch E. Low predictability of three different noninvasive methods to determine fluid responsiveness in critically ill children. *Pediatr Crit Care Med* 2015; 16 (3): e89-94. doi: 10.1097/PCC.0000000000000364.
- 15) Gan H, Cannesson M, Chandler JR, Ansermino JM. Predicting fluid responsiveness in children: a systematic review. *Anesth Analg* 2013; 117:1380-92.
- 16) Pereira de Souza Neto E, Grousseau S, Duflo F et al. Predicting fluid responsiveness in mechanically ventilated children under general anaesthesia using dynamic parameters and transthoracic

echocardiography. *British Journal of Anaesthesia* 2011; 106 (6):856-64

- 17) Kumba C (2020) Goal directed fluid and hemodynamic therapy and postoperative outcomes in children: Value of transthoracic echocardiographic aortic blood flow peak velocity variation: A multi-centre randomized controlled trial protocol. *Adv Pediatr Res* 7:35. DOI: 10.35248/2385-4529.20.7.35.
- 18) Kumba C, Willems A, Querciagrossa S et al. A Systematic Review and Meta- Analysis of Intraoperative Goal Directed Fluid and Haemodynamic Therapy in Children and Postoperative Outcome. *J Emerg Med Critical Care* 2019;5(1):1-9. DOI: [10.13188/2469-4045.1000020](https://doi.org/10.13188/2469-4045.1000020).
- 19) El Kenz H, Van der Linden P. Transfusion-related acute lung injury. *Eur J Anaesthesiol* 2013;30:1-6.
- 20) Mulder HD, Augustijn QJ, Van Woensel JB et al. Incidence, risk factors, and outcome of transfusion-related acute lung injury in critically ill children: a retrospective study. *Journal of Critical Care* 2015; 30:55-59.
- 21) Muszynski JA, Spinella PC, Cholette JM et al. Transfusion-related immunomodulation: Review of the literature and implications for pediatric critical illness. *Transfusion* 2016;00;00–00. doi:10.1111/trf.13855.
- 22) Kumba C, Querciagrossa S, Harte C, Willems A et al. A Systematic Review and Meta-analysis of Goal Directed Intra-Operative Transfusion Protocols Guided by Viscoelastic Methods and Perioperative Outcomes in Children. *Int J Recent Sci Res* 2019 ; 10 (03), pp. 31466-31471.
- 23) Claudine Kumba. Liver Transplantation in Children and Impact of Intraoperative Goal-Directed Therapies on Postoperative Outcome. Research Square 23 July 2021.  
DOI: <https://doi.org/10.21203/rs.3.rs-744584/v1>.

24) Claudine Kumba. Scoliosis in Children: Impact of Goal Directed Therapies on Intraoperative and Postoperative Outcomes. Research Square 31 July 2021.

DOI: <https://doi.org/10.21203/rs.3.rs-765785/v1>.

**25) Claudine Kumba. Patient Blood Management in Craniosynostosis Surgery. Research Square 02 August 2021. DOI: <https://doi.org/10.21203/rs.3.rs-774234/v1>.**

26) Claudine Kumba. Intraoperative Goal-Directed Therapies in Femoral and Pelvic Osteotomies in Children and In-Hospital Postoperative Outcomes. Research Square 03 August 2021. DOI: <https://doi.org/10.21203/rs.3.rs-777279/v1>.

27) Claudine Kumba. Preterm Infants in Major Abdominal Surgery and Postoperative Outcome. Research Square 30 June 2021. DOI: <https://doi.org/10.21203/rs.3.rs-669064/v1>.

28) Kumba C. Postoperative Outcome in Non-Preterm Infants Under One year Old in Non-Cardiac Surgery. Preprint from Research Square, 21 Jun. DOI: [10.21203/rs.3.rs-638904/v1](https://doi.org/10.21203/rs.3.rs-638904/v1) PPR: PPR359566

29) Claudine Kumba. "Children Aged between 1 and 3 Years in Noncardiac Surgery and Postoperative Outcome". *EC Paediatrics* 10.6 (2021): 67-74.

30) C. Kumba. Postoperative outcome in children aged between 3 and 6 years in abdominal surgery, neurosurgery and orthopedics. *Pediatric Anesthesia and Critical Care Journal* 2021;9(1):43-47  
doi:10.14587/paccj.2021.7

31) Claudine Kumba. Postoperative Outcome in Children aged between 6 and 10 years in Major Abdominal Surgery, Neurosurgery and Orthopedic Surgery. Research Square 30 June 2021.

DOI: <https://doi.org/10.21203/rs.3.rs-669076/v1>.

32) Kumba C. Major Abdominal Surgery, Neurosurgery, Orthopedic Surgery in Children aged between 10 and 18 years and Postoperative Outcome. *SOJ Pedia Clin Neonato*. 2021;1(2):1-7.000509.

# Tables

<b>Characteristic</b>	<b>N=16</b>
Mean age ± standard deviation in months	39.3±22.1
Median weight [range] in kilograms	13[5.2-22]
ASA I n (%)	1(6.3)
ASA II n (%)	3(18.8)
ASA III n (%)	12(75)
Emergency surgery n (%)	0(0)
Elective surgery n (%)	16(100)
Re-operation n (%)	0(0)
Patients with intra-operative and or postoperative complications (organ failure or sepsis) n (%)	7(43.8)
Intraoperative broncho-laryngospasm n (%)	1(6.3)
Intraoperative difficult intubation n (%)	1(6.3)
Intraoperative hemorrhagic shock n (%)	2(12.5)
Postoperative renal failure n (%)	1(6.3)
Postoperative cardio-circulatory failure n (%)	3(18.8)
Postoperative respiratory failure n (%)	2(12.5)
Postoperative pulmonary sepsis n (%)	1(6.3)
Postoperative septicemia n (%)	1(6.3)
In-hospital mortality n (%)	0(0)
Transfusion n (%)	13(81.3)
Median packed red blood cells volume in ml [range]	1[0-2]
Median fresh frozen plasma volume in ml [range]	0[0-5]
Median concentrated platelet units [range]	0[0-1]
Mean preoperative hemoglobin levels ± standard deviation in g/dL	10.1±0.9
Mean postoperative hemoglobin levels ± standard deviation in g/dL	11.1± 2.2
Median crystalloid volume in ml [range]	1300[100-2900]
Median colloid volume in ml [range]	305[60-1000]
Median length of intensive care unit stay in days [range]	7[0-16]

Median length of hospital stay in days [range]	8.5[1-17]
Median total length of hospital stay in days [range]	15[3-33]
Median total length of mechanical ventilation in days [range]	0.5[0-5]

Table 1 General Characteristics

Table 2 Co-morbidities

<b>Co-morbidity</b>	<b>number of patients (%)</b>
Cancer	8(50)
Chronic renal failure	1(6.3)