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Midline location of tumour is a risk factor for postoperative vomiting in children requiring posterior fossa tumour resection

By Susan Neufeld, Belinda Dundon, Herta Yu, Christine Newburn-Cook and Jane Drummond, J.E.

Abstract

Children requiring posterior fossa brain tumour surgery form a unique and significant neuro-oncology population. Postoperative vomiting (POV) is a problem for these children. Also, severe vomiting that is refractory to treatment has been seen clinically in these children, but it is not well described in the literature. A subgroup of children requiring surgery for posterior fossa brain tumours (n=153) from a larger six-year retrospective chart audit (n=249) at two Canadian children's hospitals were reviewed for the presence of no, mild, moderate, and severe POV. Inter-rater reliability was established at 94% following a blinded process of comparing POV severity rankings between two data collector/researchers. Discrepancies were resolved through discussion in order to establish a consensus severity score. Findings from multivariable logistic regression analyses indicated that when age and intraoperative use of ondansetron were controlled for, the location of a tumour in a midline location had no overall effect (adjusted OR=1.37, 95% confidence interval: 0.64–2.96, p=0.43), but greater odds of severe vomiting (adjusted OR=7.08, 95% confidence interval: 2.56–19.64, p<0.001). These results support theories of modulation of vomiting by the medullary midline and clinical observations that children with midline posterior fossa tumours are at greater risk for severe refractory vomiting. The development of clinical practice guidelines and further research to study the effectiveness of novel, multimodal antiemetic therapies are required for this patient population.

Les enfants nécessitant la résection d'une tumeur de la fosse postérieure située dans la région médiane démontrent un facteur de risque accru de vomissements postopératoires

Résumé

Les enfants qui requièrent une chirurgie pour une tumeur de la fosse postérieure sont une population unique et significative de la neuro-oncologie. Le vomissement post-opératoire (VPO) est un problème pour ces enfants. De plus, des vomissements sévères réfractaires au traitement ont été observés chez ces enfants, mais pas bien décrits dans la littérature. Les dossiers d'un sous-groupe d'enfants nécessitant une chirurgie de la fosse postérieure du cerveau (n=153) ont été révisés pour la présence de vomissement: aucun; léger; modéré, et sévère. Ces dossiers ont été choisis par une vérification rétrospective plus grande de dossiers (n=249), d'une durée de six années, dans deux hôpitaux pour enfants. La fidélité interjuges a été établie à 94% suivant un processus à l'insu (blinded process) en comparant le classement de la sévérité du VPO entre deux collecteurs de données/chercheurs. Les désaccords ont été résolus par une discussion pour établir un consensus du score de sévérité. Les résultats de l'analyse multivariable par régression logistique ont indiqué que lorsque l'âge et l'utilisation péropératoire d'ondansetron étaient contrôlés, l'emplacement de la tumeur dans la région médiane n'avait pas d'effet (adjusted OR=1.37, 95 % intervalle de confiance : 0.64–2.96, p=0.43) mais une plus grande possibilité de vomissements sévères (adjusted OR=7.08, 95% intervalle de confiance : 2.56–19.64, p<0.001). Ces résultats supportent les théories de modulation du vomissement par la médiane médullaire « theories of modulation of vomiting by the medullary midline » et l'observation clinique que les enfants avec une tumeur de la fosse postérieure sont à plus grand risque de vomissements sévères réfractaires. Le développement de guides de pratique clinique et plus de recherche pour étudier l'efficacité de nouvelles thérapies multimodales antiémétiques sont nécessaires pour cette population de patients.

Neuroscience nurses frequently encounter nausea and vomiting in children that are related to their disease and related cancer treatment (Hockenberry, 2004). Depending on the age of the child, tumours of the posterior fossa represent 22% to 55% of all brain tumours in children (Rickert & Paulus, 2001). Thus, children with posterior fossa tumours form a significant clinical population. Children who require posterior fossa craniotomy prior to their cancer treatment may already have experienced these distressing symptoms in the postoperative environment (Neufeld, 2002; Neufeld, Newburn-Cook, Schopflocher, Dundon, Yu & Drummond, 2009).

Some children develop severe postoperative vomiting (POV) that is refractory to treatment after posterior fossa tumour resection. Little attention has been paid in the literature to this group of children (Neufeld & Newburn-Cook, 2008). Indeed, the only discussion of severe, refractory POV following posterior fossa craniotomy comes from a case review in the adult literature (Guttuso, Vitticore, & Holloway, 2005). Given the prevalence of tumours in this location in children, understanding the characteristics of this patient population will be important to the development of prophylactic therapies and treatment protocols to provide symptom management for these children. It can be hypothesized, based on clinical observation and pathophysiologic reasoning (i.e., critical neural circuitry for vomiting comes together in the medullary midline), that children with brain tumours affecting the

medullary and cerebellar midline may be more predisposed to severe vomiting when compared to those with tumours located in other posterior fossa tumour locations.

The purpose of this paper is to identify the relationship among the midline location of posterior fossa brain tumour and the presence and severity level of POV vomiting in children requiring posterior fossa tumour resection (Figure 1). The midline location of a posterior fossa tumour can be determined preoperatively using diagnostic imaging results. Thus, if identified as a risk factor for severe vomiting, planning for antiemetic therapy and related teaching of the child and family could begin prior to surgery. The location of the tumour could then be confirmed intra-operatively and strategies continue postoperatively. If established, a relationship between midline location and severe POV would provide rationale for establishing anesthetic techniques to minimize POV, instituting novel prophylactic antiemetic therapies, and developing treatment plans for severe POV in this group.

In this study, two potential confounding variables were controlled for when examining the relationship between midline location of tumour and POV: age of child and intraoperative use of ondansetron (the only 5-HT_3 receptor antagonist used with this sample). Age less than three is a predictor of POV in other pediatric patient populations (Eberhart et al., 2004; Gan, 2006; Kranke et al., 2007). Conversely, children aged 12 to less than 17 years were less likely to vomit in the larger sample of children (n=249) requiring posterior fossa craniotomy from which the sample for this study was taken (Neufeld, Newburn-Cook, Schopflocher, Dundon, Yu & Drummond, 2009). As age was fairly evenly distributed in the sample selected for this study (i.e., did not follow a normal curve for examination as a continuous variable), quartiles were used to control for age in the multivariable analysis.

While not yet shown to be effective in preventing POV in children and variably prescribed after craniotomy (Neufeld & Newburn-Cook, 2009), intraoperative use of ondansetron has been shown to reduce POV in other pediatric populations (Gan et al., 2007). In a Bayesian meta-analysis of antiemetics and their combinations, when a 5-HT_3 receptor antagonist was combined with dexamethasone, the estimated relative risk-reduction of POV in children was 80% (Engelman, Salengros, & Barvais, 2008). In our sample, dexamethasone was used preoperatively in 88% of the children, intraoperatively in 72% of children or any time perioperatively in 96% of children. Thus, the use of dexamethasone was not controlled for in the statistical analysis due to its use in the majority of children in the sample.

Methods

Data collection

The hospital charts of all children less than 17 years of age who had experienced posterior fossa craniotomy from March 2001 to March 2007 at two children's hospitals were reviewed retrospectively. This resulted in a sample size of 249 children after screening for exclusion criteria. Exclusion criteria included postoperative intubation greater than 48 hours, craniotomy without dural opening (i.e., outside the brain), traumatic brain injury, and combined surgical procedures such as plastic surgery or otolaryngology. A subgroup of those children who required craniotomy for posterior fossa tumours was then selected based on the presence and severity of POV (n=153). Research ethics board approvals were obtained from each of two hospital sites for an examination of the patient charts specifically for the purpose of identifying the presence and severity of POV.

Measurement

A case report form and the severity rating scale for vomiting were developed specifically for the study in conjunction with a neurosurgeon, two nurse practitioners in children's neurosurgery, and a clinical nurse educator in children's oncology. Data were collected at each hospital site by the first and second authors/data collectors. Training for the two data collectors was provided using 10 patient charts. Subsequently, inter-rater reliability of 100% on the presence and severity of POV and other variables was established based on a comparison of POV ratings from five randomly selected charts. Each data collector was primarily responsible for the full review of patient charts and data abstraction from one of the two hospitals.

The midline component of the tumour was determined first through medical, preoperative diagnostic imaging reports and confirmed using the surgeon's operative report. If the two were discrepant, the operative report was used. Tumours were considered midline if they were located in the fourth ventricle, cerebellar vermis, or any combination of these two with a component within the cerebellar hemisphere. Tumours isolated in the cerebellar hemispheres and those outside of the cerebellum and fourth ventricle were classified as not midline (i.e., other). Use of intraoperative ondansetron was abstracted from the anesthesia flow sheets. Age was calculated by the data collector by subtracting the child's birthdate from the date of surgery. As the child's actual birthdate was a potential personal identifier, it was not recorded on the case report forms.

Due to their similar physiology, retching and vomiting were considered an event of POV, as recommended by Apfel, Roewer and Korttila (2002). Definitions of retching and vomit

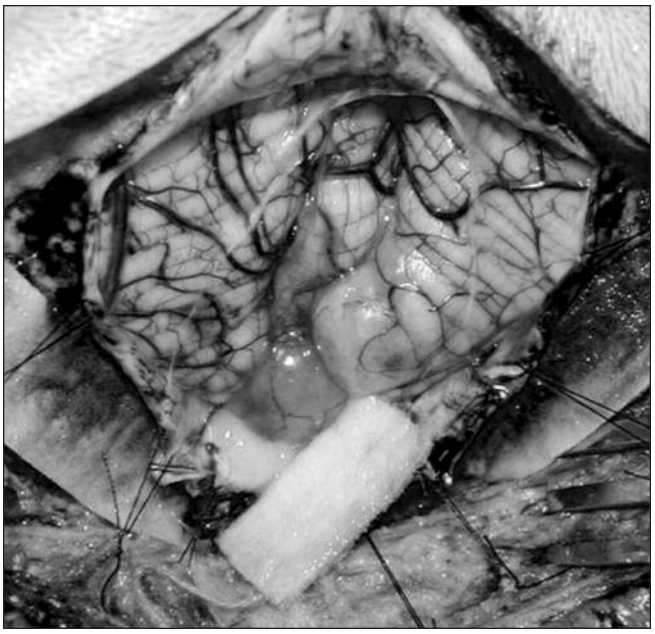

Figure 1. Midline posterior fossa tumour
Courtesy of Dr. Keith Aronyk, Stollery Children's Hospital

are needed. The time of each documented retching event or vomiting event was recorded first by examining the post-anesthesia recovery room records (usually where retching was documented) followed by the in-and-out flow sheets, and, finally, confirmed by reading the nursing notes. As a final check, timing of the administration of an antiemetic was recorded and the nursing notes were double-checked at that time for an event. Data on POV were collected from the anesthetic finish time to 240 hours after the anesthetic finish time or, if first, discharge from neurosurgical care (i.e., discharge home, transfer to the oncology unit, or to the rehabilitation unit).

After completion of the case report form, a rating of POV severity: none, mild (one to three events), moderate (> three events, responded antiemetics or self-limited), or severe (> three events, not responsive to antiemetics or self-limited) was completed by the data collector. Each data collector also rated POV severity in the other hospital group. This second rating was limited to a review of the section of the case report form that indicated presence of vomiting, antiemetic information, and related notes. Thus, the second reviewer was blind to other variables such as location of tumour, gender, or age of child. Percentage agreement of data collectors on this second review was calculated at 94%. Disagreements were resolved by discussion to arrive at a final consensus severity score to be utilized in the statistical analysis.

Table 1. Sample Characteristics

Site	n (%)
Hospital for Sick Children	123 (80.4%)
Stollery Children's Hospital	30 (19.6%)
Age	
0–<4 years	42 (27.5%)
4–<7 years	40 (26.1%)
7–<12 years	48 (31.4%)
12–<17 years	23 (15.0%)
Gender	
Female	66 (43.1%)
Male	87 (56.9%)
Location of Tumour	
Midline Component	91(59.5%)
Other	62 (40.5%)
Histopathology	
Pilocytic/Low Grade Astrocytoma	63 (41.2%)
Medulloblastoma	52 (34.0%)
Ependymoma	21 (13.7%)
Other	17 (11.1%)

Table 2. Incidence and cumulative percent of children having POV over the first 10 days

Vomiting started by:	24 hours	48 hours	72 hours	120 hours	240 hours
Incidence	70	16	7	14	7
(Cumulative Percent)	(45.8%)	(56.2%)	(60.8%)	(69.9%)	(74.5%)

Data analysis

SPSS Version 15.0 was used for data input and analysis. The sample was described by the frequency and per cent of children in each category of age, gender, location of tumour and histopathology of tumour. Incidence and cumulative percentage of POV over the first 10 days (POV overall) or discharge, whichever came first, were then calculated. The incidence and percentage of the severity ratings were then summarized. Univariate logistic regressions were first used to estimate the odds of POV overall, and severe POV when the tumour had a midline component. Finally, two multivariable regressions were completed to estimate the effect of midline location of tumour on POV overall and severe POV, controlling for age and intraoperative use of ondansetron.

Results

The characteristics of the children with posterior fossa brain tumours in the sample are summarized in Table 1. The cumulative incidence of POV over the course of data collection is shown in Table 2. POV severity ratings (Table 3) were fairly evenly distributed among the categories. The univariate logistic regression indicates that midline location of tumour was a significant predictor of severe POV (p<.001), but not significant for POV overall (p=.41). The multivariable logistic regression results (Table 5) support the univariate findings. When controlling for age and intraoperative ondansetron administration, the likelihood of POV overall was not related to midline location of tumour (p=.42). However, controlling for the same variables, children with posterior fossa tumours with a midline compo-

Table 3. Severity ratings of POV

Rating	Definition	n (%)
None	No documented vomiting or retching.	39 (25.5%)
Mild	1–3 documented events of vomiting or retching.	50 (32.7%)
Moderate	> 3 documented events of vomiting or retching self-limited or responsive to treatment.	25 (16.3%)
Severe	> 3 documented events of vomiting or retching not self-limited or responsive to treatment.	39 (25.5%)

Table 4. Univariate logistic regression: Effect of midline location of posterior fossa tumour on the development of POV overall and the development of severe POV

Outcome	Odds Ratio for Midline Location of Tumour (95% Confidence Interval)
POV Overall (mild, moderate, severe)	1.36 (0.66–2.84)
Severe POV	6.80 (2.48–18.63)**

**p<.001

nent were more likely to develop severe vomiting (p<.001). Like the study findings in the larger sample of children requiring posterior fossa surgery (Neufeld, Newburn-Cook, Schopflocher, Dundon, Yu & Drummond, 2009), children aged 12 to <17 had significantly less vomiting overall (p=.002). However, no age category was related to the development of severe POV.

Discussion

Clinical judgment suggested that POV might be frequent and severe in children after craniotomy for posterior fossa tumours. The results of this study provide clinicians with evidence that severe POV is a significant concern in this patient population, especially for children with tumours with a midline component. Physiologically, it is well known that the midline part of the brainstem is important for vomiting, as it contains a number of important regions for vomiting (i.e., the nucleus of the solitary tract, lateral tegmental field and ventral respiratory group) with complex neuro circuitry (Miller, 1999; Miller, Nonaka, Jakus, et al., 1996). Thus, the findings of this study have confirmed the hypothesis proposed from the clinical experience of the authors and physiological reasoning.

At present, clinical practice guidelines and protocols have not been studied to address the issue of severe POV for children after posterior fossa brain tumour surgery. Practices to reduce POV in children, such as careful selection of anesthetic techniques and use of efficacious antiemetics are among the strategies recommended in the Society of Ambulatory Anesthesia Guidelines for the Management of Postoperative Nausea and Vomiting (PONV) (Gan et al., 2007). Additionally, the American Society of PeriAnesthesia Nurses (ASPAN) (2006) has proposed practice guidelines for adults that address preoperative, postoperative and postdischarge PONV. However, from our experience, little has been done to consistently address the postoperative nursing care needs of children who develop severe POV following posterior fossa craniotomy.

Table 5. Results multivariable logistic regressions: Effect of midline location of posterior fossa tumour, controlling for the age of the child and intraoperative use of ondansetron on the development of POV overall and the development of severe POV

Outcome	Adjusted Odds Ratio[1] for Midline Location of Tumour (95% Confidence Interval)
POV Overall (mild, moderate, severe)	1.37 (0.64-2.96)[2]
Severe POV	7.08 (2.56-19.64)[3]**

[1] Adjusted for age in quartiles and use of intraoperative ondansetron.
[2] Age: 0–<4: 1.00 (reference variable); 4–<7:0.64 (0.21–1.95); 7–<12: 0.60(0.21-1.77); 12–<17: 0.16 (0.05–0.52)* & intraoperative ondansetron: 1.72 (0.78–3.78).
[3] Age: 0–<4: 1.00 (reference variable); 4–<7: 0.94 (0.34–2.66); 7–<12: 0.71 (0.25-2.00); 12–<17: 0.75 (0.20–2.69) & intraoperative ondansetron: 0.50 (0.22–1.13).
*p<.01, **p<.001

Further study is indicated to determine the role of intermittent administration of antiemetics for children at high risk for POV and severe POV. Currently, there is little evidence available to support best treatment for severe vomiting once it is established. Treatment of severe postoperative vomiting after posterior fossa surgery has been reported in a single published case report. Guttuso et al. (2005) successfully used gabapentin and a scopolamine patch to treat this problem in an adult. This report indicates a need for thinking beyond the usually implemented pharmacological treatments to address this problem, to novel combinations of older and more recently introduced agents. Other treatments, if acceptable to the child, parents and health care team, may also benefit in reducing POV in this population (ASPAN, 2006). These may include complementary practices such as P-6 acupuncture and aroma therapy.

Limitations

Limitations to this study include the retrospective design, which limits the type and quality of data that can be collected to what is present in the chart. Also, the results, while identifying a risk factor for severe POV, cannot provide an estimate of risk for individual children. Prospective validation would strengthen the results of the retrospective study findings reported here. However, a prospective study may prove to be costly and time-consuming. In this study between two institutions, 39 children experienced severe vomiting over the six-year study period. This small number of outcome variables limited the number of variables that we could control for in the multivariable analysis and is reflected in the wide confidence intervals of the severe POV outcome. Given the difficulty in accruing an adequate sample size, time and resources may be better spent examining solutions and researching the effectiveness of interventions such as comprehensive clinical practice guidelines that include evidence-based treatments for POV in this vulnerable patient population. Multisite collaboration will be essential in such an endeavour.

Nursing implications

As key members of the interdisciplinary team, nurses can make significant contributions to the management of POV in this population. In addition to administration of effective prophylactic and rescue pharmacological agents, nurses can implement behavioural, dietary, and developmental interventions to manage POV (Thompson, 1999). Ensuring a low-stimulation environment, mobilizing slowly with prior administration of antiemetics, advancing diet appropriately, carefully assessing cranial nerve function, using eye patches as appropriate, managing intracranial pressure when an external ventricular drain is in place, optimizing pain management and, as suggested by Gan et al. (2007), the use of a different class of antiemetics than what was used for prophylaxis may help treat established vomiting.

The development and implementation of practice guidelines may promote optimal care for this patient population and nurses are often catalysts to the development and success of such guidelines. Nausea, while not examined in the analysis for this paper due to poor documentation (Neufeld, Newburn-Cook, Schopflocher, Dundon, Yu & Drummond, 2009), also needs to be addressed in practice guidelines. Clinical assessment and documentation of frequently experi-

enced pre- and postoperative stimuli for nausea and vomiting, as well as understanding the risk factors for PONV will assist nurses in promoting the development of evidence-based guidelines and protocols for efficacious treatment of PONV (Brougham & Bolton, 2004). For example, the understanding of the relationship of midline location and severe vomiting in children with posterior fossa tumours reported here will help identify children at high risk for POV and should be included in preventive, treatment and discharge protocols.

Coordination of postoperative practices to reduce severe POV in children after posterior fossa craniotomy requires thoughtful clinical practice guidelines with the input of the health care team including nursing, surgery, anesthesia and pain management, pharmacy, dietary, and rehabilitation medicine. Early consultation of the oncology team is also essential with many of these children requiring chemotherapy and/or radiation therapy postoperatively. Communication between neurosurgery and oncology teams is also essential in identifying which strategies worked for individual children so that symptom management is optimized throughout the continuum of care.

In conclusion, vomiting is a postoperative problem for children after posterior fossa tumour resection. During the study period, almost 74% of the children had at least one vomiting episode. Moreover, 25% of children exhibited severe vomiting. Children with a component of their tumour located in the midline were at greatest risk for severe vomiting. Knowledge of risk factors for severe POV, such as midline location of tumour, will help us target prevention and intervention strategies to those groups of children at risk for this adverse outcome. Future research in this area will require ongoing multisite collaboration and novel approaches to prevention and treatment. Research outcomes must also be carefully chosen, as we suggest that the risk factors for the development of POV overall are different than those for severe POV.

About the authors

Susan Neufeld recently completed her PhD in nursing at the University of Alberta. She was a strategic doctoral trainee in the Canadian Child Health Clinician Scientist Program (CCHCSP).

Correspondence regarding this article should be addressed to Dr. Susan Neufeld, e-mail: ***smn@ualberta.ca***

Belinda Dundon and Herta Yu are neuroscience nurses at the Hospital for Sick Children, Toronto, ON.

Christine Newburn-Cook and Jane Drummond are professors in the Faculty of Nursing at the University of Alberta.

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