Pre and Postoperative Diarrhoea Associated with Neuroblastoma Resection – A Systematic Review of Published Studies

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Abstract

Neuroblastoma is a malignant tumour affecting 10.5/1 million children annually. It arises from sympathetic nervous system precursor cells and is most frequently found in the adrenal gland and abdominal paravertebral ganglia. Diarrhoea as a presenting symptom of neuroblastoma is uncommon and usually linked to vasoactive intestinal peptide (VIP) tumour secretion. Even more rarely, postoperative diarrhoea may follow neuroblastoma tumour resection. Published studies generally associate postoperative diarrhoea with subadventitial tumour resection. These findings are however based on a handful of reports. This systematic review therefore aims to analyze the true incidence of postoperative diarrhoea and its morbid correlation with the extent / type of surgical resection. Pubmed / Embase databases were searched according to PRISMA guidelines. Final analysis consisted of 16 studies: N=779 patients. Postoperative diarrhoea was significantly more common in all patients who underwent subadventitial resection compared to non subadventitial resection, $p<0.001$ (OR 25.9, 95% CI 9.3–72.4). 5-year survival rates were equivalent in both groups. Preoperative diarrhoea was rarely reported in studies and always strongly linked to elevated VIP secretion. In the majority of neuroblastoma patients, preoperative diarrhoea ameliorated after gross tumour resection with elevated VIP normalized. The operative technique of subadventitial neuroblastoma resection portends significant risk(s) of post operative diarrhoea not seen in those patients undergoing other classical methods of tumour resection with 5-year survival rates strikingly similar. These findings affirm that subadventitial tumour resection should be avoided when undertaking surgery for neuroblastoma to minimize the risk(s) of persistent postoperative diarrhoea.

Keywords: diarrhea; neuroblastoma; subadventitial resection;

Abbreviations: VIP – vasoactive intestinal peptide

Introduction

Neuroblastoma (NBL) is the most common malignant extra cranial solid tumour in infancy affecting some 10.5 / 1 million children per year [1]. It arises from sympathoadrenal precursor cells and is therefore most frequently found in the adrenal gland and abdominal sympathetic ganglia [1, 2]. According to the International Neuroblastoma Staging System (INSS) tumours are graded from Stage I to IV(s) [3]. Furthermore, tumours are classified into different risk groups (very low, low, intermediate, and high risk) according to the International Neuroblastoma Risk Group (INRG) [4]. Neuroblastoma intricately wraps itself around major vascular structures and abdominal organs with metastases often to bone, bone marrow, and distant organ sites [1, 5]. Curative treatment includes radical excision of primary tumour with deployment of neoadjuvant chemotherapy, postoperative radiotherapy, and targeted immunotherapy [5-8].

Watery diarrhoea, with hypokalaemia and achlorhydria (WDHA-syndrome) due to active secretion of vasoactive intestinal peptide (VIP) from tumour is an unusual manifestation of neuroblastoma [9]. It has been estimated that less than 1% of all neuroblastoma tumours display evidence of VIP secretion [10]. Diarrhoea as the sole presenting symptom of neuroblastoma is thus rarely observed [6, 10]. By contrast, postoperative diarrhoea may accompany resection of neuroblastoma [5, 8, 11-13].

Subadventitial neuroblastoma resection was first pioneered by Kiely in 1993 [12]. Neuroblastoma tumours usually invade only the vessel tunica adventitia but not tunica media, and this key observation led Kiely to propose a new technique for radical excision of tumours where the surgical plane of dissection is precisely located between the tumour mass itself and tunica media in the subadventitial area [14].

Subadventitial resection has been supposedly linked with post operative diarrhoea [7]. In such patients the incidence of diarrhoea (30%) is reportedly higher, persistent and refractory to effective treatment(s) [5, 7]. Detailed comprehensive reporting on postoperative diarrhoea in neuroblastoma studies is however distinctly lacking. Against this background of controversy, the aim of this systematic review study was to comprehensively analyse the 'real world' incidence of diarrhoea occurring in neuroblastoma patients both pre and postoperatively. We hypothesized that subadventitial neuroblastoma resection would be associated with more frequent postoperative diarrhoea. We also sought to study survival outcomes of neuroblastoma patients undergoing subadventitial resection vs. non subadventitial tumour resection.

Material and Methods

Identification and Selection of Studies

A comprehensive search in PubMed and Embase databases was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [15]. The following terms were used as keywords: 'neuroblastoma' in combination with 'diarrh(o)ea' or 'bowel function' or 'Kiely technique' or 'subadventitial resection'. All articles from inception published up to October 28, 2022, were included in the study review.

Inclusion and Exclusion Criteria

This study included all original articles reporting on neuroblastoma-associated diarrhoea. Non-English language papers and case reports (<3 patients) were excluded with title and abstract screening. Duplicate data from the same centres or research groups were excluded or combined (Figure 1).

Data Extraction and Analysis

Identified papers were independently reviewed by two study authors (SA and AR). Data reporting tumour stage and diarrhoea status of patients both pre and postoperatively were extracted from all the publications. The final selection was approved by the senior author (PDL).

Statistical Analysis

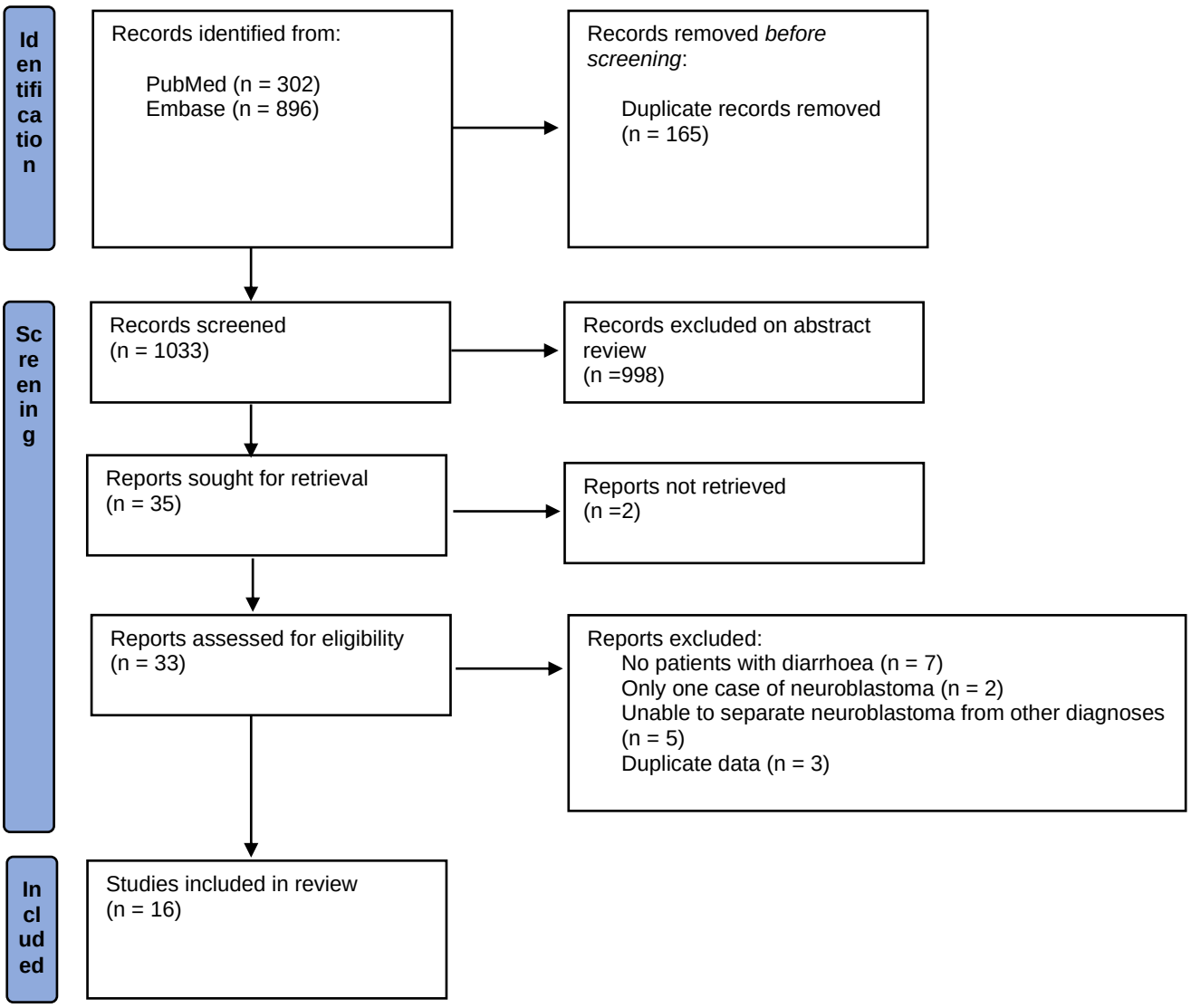
Chi-Square and Fisher's exact tests were used to analyse categorical variables. A significance level of $p \leq 0.05$ (two-tailed) was set. No attempt to replace missing values was made. Analyses were performed using JMP Pro, version 16.1.0 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

The original search identified 1198 studies. Duplicates were excluded and screening of titles and abstracts was made. After that, 33 articles met the eligibility criteria and were selected for full text review. The final analysis consisted of 16 studies with a total 779 NBL index patients (Figure 1). These articles were published between the time era(s) 1982—2015 [5-13, 16-23].

Postoperative diarrhoea was significantly more common in all neuroblastoma patients who had undergone subadventital tumour resection compared to non subadventitial resection $p<0.001$ (Table 1). Preoperative diarrhoea was observed in some 46 patients and virtually all of these index cases had VIP secreting tumours based on elevated serum VIP values and/or intra-tumour VIP expression as determined and assessed by immunohistochemistry. Only two of these patients later suffered from persistent postoperative diarrhoea following tumour resection.

Figure 1. PRISMA study selection flow diagram.



	No diarrhoea	Persistent postoperative diarrhoea	Odds Ratio	95% Confidence Interval	P Value
Subadventitial resection (n=301)	247 (82.1%)	54 (17.9%)	25.9	9.3 – 72.4	<0.0001
Non subadventitial resection (n=478)	474 (99.2%)	4 (0.8%)	reference value		

Table 1. Incidence of postoperative diarrhoea after neuroblastoma resection.

Survival data we sought to interrogate were sparsely available from eligible studies and here only a single study recorded outcomes for subadventitial and non subadventitial resection in advanced stage neuroblastoma. Stage IV neuroblastoma survival rates were reported to be some 30% equivalent with both the subadventitial and non subadventitial techniques – i.e. non significant [5].

Discussion

This systematic review study has clearly demonstrated that postoperative diarrhoea following surgery for neuroblastoma is strongly associated with the subadventitial resection technique. We speculate this is due to autonomic nerve damage caused by extensive subadventitial tumour resection. Preoperative diarrhoea by contrast is almost exclusively associated with VIP-secreting tumours, and cessation of diarrhoea following surgical resection can generally be anticipated in most cases.

Postoperative diarrhoea is noted to occur particularly after the surgical resection of advanced neuroblastoma tumours. Kiely et al. reported postoperative diarrhoea in up to 30%

of index cases undergoing major operation [5, 7, 12]. In this study reported from Great Ormond Street Hospital subadventitial neuroblastoma tumour resection was exclusively performed. The authors further reported that postoperative diarrhoea was mainly observed in those patients where the surgical field of resection was extended cephalad to coeliac trunk regions and the superior mesenteric artery. Also, postoperative diarrhoea was refractory to any treatment and persisted in the majority [5]. It is hypothesised that surgical resection extending to this vital anatomical region damages the enteric autonomic nervous system thus dramatically altering gut transit function [7]. By contrast non subadventitial resection techniques with the surgeon herein adopting an extravascular plane shelters the autonomic nerve plexus and ganglia without consequential post operative diarrhoea [5, 12].

Of key importance in this study, we further observed no significant difference(s) in patient survival comparing the subadventitial tumour resection technique vs. non subadventitial methods [12]. Tian et al. [24] interestingly reported data on some 71 stage III and IV neuroblastoma patients who underwent gross total resection deploying a non subadventitial resection technique. Whilst almost half of the patients experienced diarrhea this was only a temporary phenomenon in this study persisting until the fifth post operative day [24]. In a further report from Saudi Arabia, preoperative diarrhoea was noted in 20 index patients and fully resolved in all cases with tumour resection [20]. In 2007 Kiely et al. [5] showed 5-year survival outcomes with the subadventitial resection technique to be 85% in stage III and 30% stage IV tumours with postoperative diarrhoea recorded in 30% of cases. In 2004, La Quaglia et al. [8] at Memorial Sloan Kettering Hospital USA reported their institutional data with surgical resection in stage IV neuroblastoma reporting a 5-year survival rate of some 50% cases. Only two of 143 patients (1.4%) in La Quaglia's study had postoperative diarrhoea.

Diarrhoea occurring i.e., pre and preoperatively is encountered rarely in neuroblastoma. Studies, our own included here with other published work show that elevated VIP secretion

is associated with troublesome diarrhoea. In index case(s) of preoperative diarrhoea with a VIP neuroblastoma tumour this often is cured with resection [9, 16, 18]. However, postoperative diarrhoea is a substantial morbid risk strongly linked to subadvential neuroblastoma resection. No benefit in patient survival is shown from this study.

Strengths and Limitations

To the best of our knowledge, this is the first systematic review on this key topic. The report convincingly shows that subadventitial neuroblastoma resection carries substantial risk(s) of troublesome post operative diarrhoea. We additionally report the ‘real world’ incidence of VIP secreting diarrhoea in primary neuroblastoma and its anticipated resolution with tumour resection. We fully acknowledge the study has certain inherent limitations due to the variations in methods of data reporting from all the eligible included published studies, especially those lacking data on detailed radiological imaging and tumour biology.

Conclusion

Postoperative diarrhoea is strongly linked with the subadventitial operative resection technique whereas preoperative diarrhoea encountered rarely in neuroblastoma is usually VIP-induced and cured by gross resection. Non subadventitial neuroblastoma resection is rarely associated with postoperative diarrhoea and crucially survival rates are similar comparing surgical techniques. Subadventitial resection for neuroblastoma should be avoided where possible to minimize the risks of morbid and persistent postoperative diarrhoea.

Author Contributions

The study was originally conceived and designed by PDL. SA and AR conducted the literature review, data collection, analysis, and interpretation under supervision by PDL. The manuscript was drafted by SA and AR. All authors participated fully in drafting the manuscript, revisions and approved the final version submitted manuscript.

Declaration of Competing Interest

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