The assessment and management of pain in children with GuillainBarré Syndrome in a sub-Saharan setting

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Abstract

Introduction: Neuropathic pain is challenging to manage in children compounded by inappropriate assessment tools. The lack of evidence-based pain control guidelines for children results in clinicians deferring to expert opinion and personal preference. Children with Guillain-Barré Syndrome are particularly at risk is of neuropathic pain. **Objectives and Methods:** This is a retrospective study of children with Guillain-Barré Syndrome who were admitted to Red Cross War Memorial Children's Hospital, Cape Town, South Africa over a 10 year period. The study reviewed their pain assessment and management practice. **Results:** Eighty-four children were identified with Guillain-Barré Syndrome. 76% had symptoms of pain and 53% had breakthrough pain reported. Standardised pain rating scales were used in 3 patients. A mean of 2.7 analgesics were used per patient. Carbamazepine and gabapentin, were utilised in 27 and 20 patients respectively. The use of gabapentin increased 73% per annum from 2009. There was no statistical difference between these two groups for length of hospital stay or long-term disability. **Conclusion:** This study identified a significant gap in the assessment of pain in children with Guillain-Barré Syndrome. Tools to adequately assess pain are needed, especially in immobile and non-verbal children. Management of pain revealed a high use of adjuvant drugs. The dramatic increase in the use of gabapentin related to clinician preference and was not supported by any evidence. Clinical outcomes for both the carbamazepine and the gabapentin group were no different.

Kewords: Pain Assessment tools; Gabapentin; Carbamazepine; Children; Acute Inflammatory demyelinating Polyradiculoneuropathy; Guillain-Barré syndrome.

Introduction

The prevalence of moderate to severe pain in the paediatric hospital setting is high [1]. Pain management and analgesia is often suboptimal due to lack of training and knowledge, negative attitudes towards analgesics, inappropriate assessment of pain and the lack of algorithms to guide clinical practice [2, 3, 4, 5]. In Africa, there are additional challenges of access to facilities, affordability and sustained availability of medications. As a result, paediatric pain relief often falls short of World Health Organization standards [6, 7]. Neuropathic pain, is increasingly recognized to occur in children and reported in diseases such as complex regional pain syndrome, spinal injuries, postoperative neuropathic pain, cancer related neuropathies, human immunodeficiency virus (HIV) neuropathy, and autoimmune conditions such as Guillain-Barré Syndrome, or acute inflammatory demyelinating polyradiculoneuropathy (AIDP) [8, 9, 10].

In Guillain-Barré Syndrome the sensory changes include pain and paresthesia. The pain experienced is both nociceptive and neuropathic and is documented in up to 80-90% of patients, of whom two-thirds are considered to be severe [11, 12, 13, 14]. The natural history is variable in children with a mean length of time to symptom free recovery of 67 days. Improved pain control impacts on overall patient care and the illness experience [15, 16]. This is thought due to improved coping mechanisms, decreased stress and anxiety,

improved capacity to deliver acute and longterm rehabilitation, all of which may reduce the length of hospital stay and overall illness duration.

There are no clear guidelines to manage neuropathic pain in children, which has led to anecdotal practices and polypharmacy [3, 4, 17, 18]. Combination therapy and adjuvant therapies such as tricyclic antidepressants, antiepileptic drugs (AEDs), calcitonin and local anaesthetics are used in conjunction with United State Food and Drug Administration (FDA) approved analgesics [19, 20, 21].

Whilst AEDs such as carbamazepine, gabapentin and pregabalin are used for pain control, there is a lack of class one studies [19, 20, 22, 23, 24]. Small study size trials support the efficacy and safety of these drugs as analgesics, and there are reports that they are at least as effective as opioids for neuropathic pain relief with the additional advantage of reducing opioid requirements [25, 26, 27, 28]. This study reviewed the trends in the assessment and management of pain in children admitted to a tertiary centre in sub-Saharan Africa with Guillain-Barré Syndrome.

Methods

This was an observational retrospective study of clinical practice from 1st January 2002 to 31st December 2012, based at the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa. This is a university affiliate tertiary teaching hospital. It is the largest children's hospital in sub-Saharan Africa. The centre offers specialist and sub-specialist care to the paediatric population from the Western Cape and wider afield. Children with Guillain-Barré Syndrome are managed according to current standard recommended guidelines. Children are clinically assessed to have pain, typically based on parental, nursing and ancillary staff feedback, are prescribed paracetamol with tilidine as a rescue dose for breakthrough pain. As part of standard hospital policy morphine is used for moderate to severe pain.

Current practice in our centre for pain control of patients with Guillain-Barré Syndrome is the off-label use of the antiepileptic drugs, namely carbamazepine and gabapentin. Either agent is initiated following the diagnosis of Guillain-Barré Syndrome when pain, or the perceived risk of pain, is present. The later relates to the child who cannot express that they are in pain, for example whilst they are ventilated, or if they have profound motor impairment. Carbamazepine is titrated up to a maximum of 10-15 mg/kg/day over 2 to 3 weeks and gabapentin up to 40mg/kg/day over 2 weeks. Maintenance dose is based on the point of apparent pain control. Treatment is weaned off over 2 weeks during the rehabilitation period or at the time of discharge, when pain is no longer a complaint. As such the baseline acute pain care for these children is standard (paracetamol, tilidine and morphine) and the variable adjuvant drug decided upon by the attending clinician is either carbamazepine or gabapentin. This allowed us to analyse the sample in three distinct groups: patients who received carbamazepine, pa-

tients who received gabapentin and those who received neither agent. The groups were compared for duration of documented pain, severity, length of hospital stay and outcome.

Inclusion criteria: Children admitted over the study period (January 2002 to December 2012) between 1 month and 12 years of age with a confirmed diagnosis of Guillain-Barré Syndrome, based on history and clinical examination, cerebrospinal fluid (CSF) findings and special investigations (neuroimaging and or nerve conduction studies) [29].

Exclusion criteria: Acute flaccid paralysis (AFP) due to an alternative cause such as acute transverse myelitis or non-polio enterovirus infections. Also, the dual use of gabapentin and carbamazepine for maintenance pain control since this precluded comparison of the outcome results from a single intervention and study numbers proved too small for this category.

Data collected included patient demographics, disease pattern and course, standard and adjuvant analgesic interventions, and the severity of illness. The medical records were reviewed for documentation of the analysis of pain assessment either via a formal pain score (e.g. FLACC [30] or COMFORT [31]) (Appendix A), as an annotation in the medical, nursing or rehabilitation staff medical records, or through the frequency of additional analgesic doses. Data was recorded from those children who underwent cerebrospinal fluid screening (CSF), nerve conduction studies and magnetic resonance imaging (MRI). Immediate outcomes were documented with regards to duration of stay and resolution of respiratory compromise. All data were captured using Epidata and was analyzed using Matlab Statistics program.

Results

Between 2002-2012, 84 patients were admitted to RCWMCH with Guillain-Barré syndrome. The group demographics are summarized in Table 1. Sixty-five (76%) of the children had symptoms of pain recorded in their medical records, predominantly by the rehabilitation therapists. However, the severity of the pain could not be quantified due to suboptimal assessment of the pain and inadequate use of objective pain rating tools. Pain rating tools were only used in 3 patients. More than half of patients had breakthrough pain (53%) reported in their folders with the majority of this documented in relation to physiotherapy sessions. A mean of 2.7 analgesics were used per patient. Other modalities to relieve pain were also used inconsistently and to a lesser extent. The characteristics of analgesic usage are demonstrated in Table 2.

The use of analgesics paracetamol, morphine and tilidine remained constant throughout the study period. From 2002 until 2008 all patients with documented pain were prescribed carbamazepine but from 2009 gabapentin was the preferred agent, and almost completely replaced carbamazepine. From 2009, the overall trend of gabapentin usage was dramatic with an average increase of 73% per

Table 1 Demographics of patients admitted to RCWMCH with GBS from 2002-2012

Characteristic	Result Total n = 84	Carbamazepine n = 27	Gabapentin n = 20	Neither Carbamazepine nor Gabapentin n = 37	P value
Age (median)	52 ± 42 months range: [8-144]	60 ± 42 months range: [8-144]	48 ± 35 months range: [13-138]	52 ± 35 months range: [11-144]	0.41
Male:Female (percentage ratio)	50:50	45:55	55:45	51:49	-
Length of hospital stay (median days)	14 ± 43 range = [2-121]	45 ± 33 range = [5-119]	48 ± 36 range = [8-121]	10 ± 15 range = [2-90]	0.85
Proportion needing ICU	41%	59%	64%	17%	0.62
Length of ICU stay (median days)	21,5 ± 33 range = [1-83]	31 ± 24 range = [1-83]	26 ± 24 range = [1-83]	15 ± 30 range = [2-75]	0.18
Proportion needing ventilator support	31%	52%	50%	8%	0.87
Proportion needing a tracheostomy	28%	52%	45%	1%	0.62

Table 2 Characteristics of pain assessment and analgesic usage

Pain characteristic	Total Study Results	Carbamazepine	Gabapentin	Neither Carbamazepine nor Gabapentin	P value*
Number of patients	n=84	n=27	n=20	n=37	
Number of patients with documented pain	76% (n= 65)	86% (n=24)	100% (n= 21)	54% (n= 20)	0.67
Pain rating tools used	FLACC scale (2), Visual Analogue (1)	3% (n= 1) Visual Analogue	14% (n= 2) FLACC scale (2)	0% (n= 0)	-
Mean number analgesics used	2.3 ± 1.8 range = [0-9]	3.2 ± 0.8 range = [2-5]	3.2 ± 0.8 range = [2-5]	1.2 ± 2.1 range = [0-9]	0.76
Duration pain documented (median days)	4 ± 8 range = [0-59]	13.4 ± 12 range = [2-56]	12.7 ± 13.4 range = [2-59]	4.2 ± 4.2 range = [1-20]	0.9
Number of patients experiencing breakthrough pain	55% (n= 47)	79% (n= 22)	77% (n=16)	24% (n= 9)	
Agent used to treat breakthrough pain					
Tilidine	84%	87%	88%	71%	
Paracetamol	9%	4%	6%	14%	
Morphine	2%	0%	6%	0%	
Ketamine	4%	0%	2%	0%	
Not documented	1%	9%	0%	15%	
Allied therapy used					
Physiotherapy	95%	100%	100%	89%	
Occupational therapy	85%	97%	100%	68%	
Speech Therapy	52%	79%	86%	14%	
Play	9%	7%	27%	0%	
Music	5%	3%	18%	0%	
Aromatherapy	2%	3%	9%	0%	
Primary caregiver at bedside	93% (n= 80)	93% (n= 26)	86% (n= 18)	95% (n= 35)	

*P - Value: Comparison between Carbamazepine and Gabapentin treatment groups only.

annum (Figure 1). Of 49 children, 20 received gabapentin, 27 carbamazepine and 2 subsequently received both agents separately.
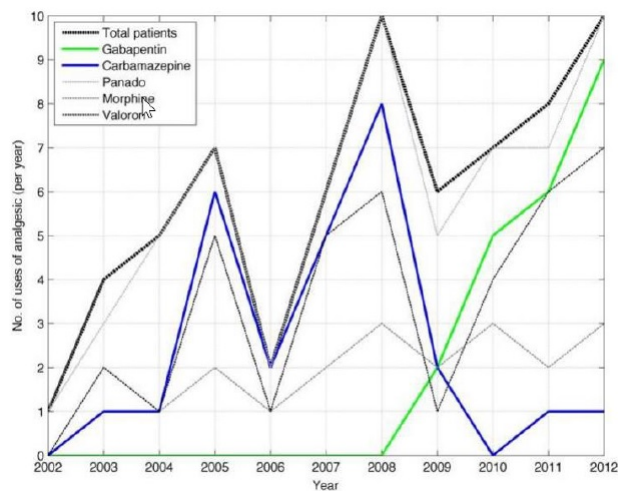

Figure 1 Number of times each analgesic initiated per annum for children with Guillain-Barre Syndrome.

For the whole group there was no statistical difference in any of the clinical interventions between the two AED groups. The children treated with carbamazepine received a mean dose of 4.3mg/kg/day (range 1.5-10) for 31 days (range 5-75) and those who received gabapentin received 9.38mg/kg/day (range 3-15) for 47 days (range 7-123 days). Thirty-seven children did not receive regular prophylaxis with either AED, these children tended to have a shorter, less severe course (p=0.0001). CSF was performed on 79 of the 84 patients with abnormally raised protein in 53%. Nerve conductions studies were performed in 38 patients and were supportive of the diagnosis in the majority (95%). Twenty-five patients underwent spine MRI, 10 were normal and the remaining 15 had enhancement of the nerve roots. Neuroimaging was performed when there was diagnostic concern, such as for the children on artificial ventilation who were paralysed and could not be formally neurologically assessed.

Discussion

Pain measurement in children is difficult [15, 31]. Pain assessment tools are not standardized and as this study illustrates, this forms a major barrier to real understanding of the degree of pain suffered by children and the efficacy of the interventions used to control the complications. Appendix A summaries the pain tools which could be considered in these children. The few validated tools are mostly used in acute settings and resource equipped settings [15, 32]. These tools may be less reliable in an African setting due to ethnic variation and differences in beliefs. There are no observational tools developed for measuring neuropathic or chronic pain in children [9, 32, 33]. Self-reporting is considered the most reliable method, especially in the setting of chronic pain [32, 34, 33]. But children, especially manijky of those in this cohort, would be too young to self-report, and those old enough may not be able to self-report for the initial period due to being sedated and/or ventilated [28]. The autonomic dysfunction which occurs in patients with Guillain-Barré syndrome would be a significant confounding factor when considering pain rating tools that rely on physiological measures [28]. Inadequate measurement

and assessment of pain during the study period limits definitive or useful comment on the degree of pain experienced by these children.

Neuropathic pain is a difficult entity for a clinician to manage. More than half the patients in this study were prescribed either gabapentin or carbamazepine as adjuvant analgesics. From the modalities recorded there was no difference in the apparent efficacy or safety for either agent. Whilst there is slightly more data to support gabapentin, overall the evidence is limited for both, especially in children [22, 24]. There are two class I studies assessing the efficacy of gabapentin in adults with GuillainBarré syndrome. The first reviewed 18 adults in a randomized, doubleblinded, placebo-controlled crossover study [25]. In addition to a numerical pain score, the amount of adjuvant analgesia with fentanyl was used as a measure of pain control. The study period was for 7 days and a significant reduction in pain and adjuvant therapy was evident during the gabapentin periods. The second study reviewed 36 adults with GuillainBarré Syndrome in a randomized, prospective, double-blinded, placebocontrolled study for patients in an intensive care setting who were ventilated [26]. Patients were allocated to receive gabapentin, carbamazepine or placebo. The group concluded that both AEDs were more effective than placebo and that gabapentin was more effective than carbamazepine for decreasing pain and the need for adjuvant analgesia. Cohort sizes and duration of intervention were limiting factors for both these studies. The systematic review by Pena et al concluded that there was no robust evidence to recommend a single treatment option to manage pain in people with Guillain-Barré Syndrome [23]. The group supported the need for further clinical studies with larger numbers, longer duration of monitoring and more effective measures to document intensity of pain objectively [23]. A Cochrane review also could not conclude that there was sufficient evidence to support use of a specific pharmacological intervention, the follow-up meta-analysis 2 years later conclude the same [24, 35]. The authors concluded that whilst reductions in pain severity were evident with both gabapentin and carbamazepine compared to placebo, the evidence for this remained limited and of low quality, further highlighting the need for larger, well designed randomised controlled trials.

Carbamazepine is associated with adverse effects related to its toxic metabolite and drug-drug interactions [36]. In the sub-Saharan setting due to the high prevalence of HIV, carbamazepine is ideally avoided in combination with antiretroviral therapy to avoid AED toxicity and HIV treatment failure [37]. In this setting, Gabapentin has a more favourable pharmacokinetic profile as it has an equivalent bioavailability to carbamazepine, is excreted unchanged via the kidneys, does not induce cytochrome p450, has fewer drug interactions and an overall better side effect profile [38].

Gabapentin is approved by the FDA for use in postherpetic neuralgia and focal epilepsy, off-label usage in both adult and paediatric practice has extended to various neuropathic pain conditions such as complex regional pain syndrome, post-operative neuralgia, burns, neuropathies related to cancer and HIV, and autoimmune syndromes such as GuillainBarré Syndrome [39]. Despite the lack of class I evidence, the usage of gabapentin on and off-label has increased. The increasing trends of gabapentin usage in this study occurred due to clinicians' personal preference. The widely accepted anecdotal support of gabapentin needs more data to support a stronger recommendation for use.

Conclusion

This study draws to light two important issues. Firstly, the need for improvement and education in the use of standardized, objective and reproducible tools to rate pain on a regular basis in patients with GuillainBarré Syndrome. Secondly, with the increase of the use of gabapentin to control pain associated with Guillain-Barré Syndrome in children in our setting, the safety and efficacy needs to be established in comparison to other AEDs such as carbamazepine and pregabalin. This information will be vital in generating guidelines and protocols for pain management in various painful conditions and will in turn improve the way that we manage children experiencing pain with Guillain-Barré Syndrome.

Aknowledgments

Appendix A. Comparison of pain tools used in children

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Competing interests

The authors have declared that they have no competing interests.

Authors' contributions

All the authors contributed to data collection and also critically reviewed the manuscript. The final version of the manuscript was approved by all the authors.

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Appendix A - Comparison of Pain Tools used in Children

TOOL	USES	PROS	CONS	COMMENTS
FLACC [30]	>11yr; Acute; Post op; Minor non-invasive procedures	Validated in children; Class I evidence; Observational Simple; Low cost;	Acute pain	Use in measuring; neuropathic/chronic pain; use has not been established; Paralysis.
COMFORT [40]	Newborn-17yrs; Ventilated patients	Class II evidence; Validated in ventilated patients; Can be used in critical care/PICU setting; Good inter-rater variability; Observational; Simple; Low cost.	Acute pain	Ventilated/sedated patients.
VAS Numerical FACES [41]	Verbal child; Acute or chronic pain	Self-report regarded as best tool in chronic pain	Requires awake and orientated patient	Ventilated/sedated patients; Challenging in young or paralysed children.
LANSS [42]	Adult Neuropathic pain	Specific	Questionnaire format; Complex.	Challenging in young or paralysed children
CHEOPS [43]	1-7yrs; Acute and chronic pain; Post op; fractures; sickle cell disease; immunisations.	Proposed 1month-17yrs; Observational; Valid.	Better in acute setting	Paralysis
APPT [44]	8-17 yrs.	Proposed 2-68 yrs.; Valid; Reliable; Sensitive; May be able to differentiate between neuropathic and nociceptive pain	Adolescents; Acute pain.	Challenging in young or paralysed children; Translation of lists; Sedation/ventilation.
NCCPC-R [45]	3-18 yrs.; With neurological impairment; Children who are unable to speak	Incorporates physiological variables; Simple; Cost effective.	Neurocognitive impairment	Autonomic instability may occur as part of GBS; Paralysis.