Impaired mobility associated with an increased likelihood of death in children: a systematic review

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Abstract

Improved identification of children with increased likelihood of death can support appropriate provision of integrated palliative care; this systematic review aims to consider immobility and the associated likelihood of death, in children with disabilities, living in high-income countries. Two reviewers independently searched Medline, Embase, Cochrane Library, OpenGrey, Science Citation Index (1990 to 2016) for studies that reported hazard ratios (HR) and relative risk (RR) for likelihood of death related to impaired mobility. Nine papers were included. Three studies reported functioning using the Gross Motor Function Classification Scale (GMFCS); remaining studies reported measures of functioning unique to the study. The strongest single prognostic factor for likelihood of death was 'lack of sitting ability at 24 months', HR 44.4 (CI 6.1 to 320.8) followed by GMFCS V HR 16.3 (CI 5.6 to 47.2) and 11.4 (CI 3.76 to 35.57) and 'not able to cruise by 24 months' HR 14.4 (CI 3.5 to 59.2). Immobility is associated with increased risk of dying over study periods, but different referent groups make clinical interpretation challenging; overall, quality of evidence is

moderate. The findings suggest that immobility can indicate suitability for integrated palliative care, for children with disabilities.

It is estimated in the World Health Report on Disability (2011), that in 2004, around 13 million children, under the age of 14 years, were living with severe disability (World Health Organization, 2011). The term 'disability' is now viewed as an umbrella term for impairments of body functioning (World Health Organization, 2012). Due to either increased survival, changes in disability definitions, or survey procedures, prevalence of disability in high-income countries is increasing (Halfon et al., 2012; Friebert and Williams, 2015).

For some, there is a significant burden of illness (Read et al., 2012) and uncertainty, since health may be unpredictable and unstable (Horridge, 2015). Variations in definitions and prognostic criteria can hinder identification of children who are considered life limited (Friebert and Williams, 2015). In the UK, children with 'irreversible but non-progressive conditions causing severe disability, leading to susceptibility to health complications and likelihood of premature death' are considered to be life limited (Together for Short Lives, 2013), and further delineation is available in a directory of life limiting conditions (Hain et al., 2013). However, while prevalence (or identification) of children with life limiting conditions is also increasing (Fraser et al., 2012), for children with severe

impairments of body functioning (World Health Organization, 2012) the focus is often on enhancing participation and improving quality of life (Rosenbaum, 2015) and consideration of likelihood of death is sometimes seen as incongruent with this focus, and may be given little consideration. While severe impairments are associated with death in childhood (Wolfe et al., 2014), prognostic uncertainty remains, and suitability for palliative care, therefore, uncertain.

Children with recognised life limiting conditions, and their families, can benefit from palliative care, as an active approach to holistic care from diagnosis, regardless of whether treatment interventions are available; this approach involves giving support to the family as well as the child, and can be implemented even when resources are limited, such as by the team that know the child best, even when specialist palliative care teams are not available (World Health Organization, 2015). However, children with severe impairments are not always recognised as needing palliative care due to the uncertainty of prognosis, and the fact that many survive into adulthood. Unfortunately, this puts some at risk of not receiving appropriate and timely palliative care, which, as for many chronic health conditions, can be of long term benefit (Siouta et al., 2016).

Palliative care in its different guises ranges from a philosophy of care to specialist services (Hain and Wallace, 2008), but is recognised under the United Nations human right to health. Palliative care for children with chronic health conditions, and their families, can help meet the increasing health needs of cumulative disabilities and decreasing quality of life (Dallara et al., 2014; Graham and Robinson, 2005; Viallard, 2014). However, this needs to be introduced early for maximising benefit such as improved symptom management, support for decision making, and reduced interventions at end of life (Hauer and Wolfe, 2014; Walter et al., 2013). For bereaved parents, lack of support at end-of-life, places them at increased risk of long-term psychological and physical morbidity (Rosenberg et al., 2012).

While there is variability in local availability of palliative care services, and lack of consensus in the definition of integrated palliative care, it is generally accepted that palliative care is not a standalone intervention. An integrated approach, aimed at improving quality and quantity of life, is known to increase the quality of care and support health care professionals (Ewert et al., 2016). Even in the absence of focussed palliative care services, advance care planning for this population, is an important means of managing uncertainly and driving up standards in children's palliative and end-of-life care (Brook and Hain, 2008).

This dual planning concept, involves making multiple plans for care, and using the one that is most appropriate for the circumstances at the time (Villanueva et al., 2016).

In trying to identify children with life limiting conditions, research has usually focused on either medical diagnoses (Hain et al., 2013), or impairments of body functioning (Strauss et al., 2000); however potentially both features could be used together to improve estimation of prognosis. For example, while spastic quadriplegic cerebral palsy [ICD 10 G80.0] and mixed cerebral palsy syndromes [ICD10 G80.0] are identified as life limiting (Hain et al., 2013), not all children with these diagnosis will die in childhood, and consideration of functional status (activity, performance and participation) is important (Bergstraesser et al., 2013). There may be specific impairments of functioning, routinely measured, within these diagnostic categories that may be useful in identifying children at increased likelihood of death. Attention to both diagnosis and impairments to functioning may therefore help health care professionals further define the population with an increased probability of death, and facilitate earlier interventions.

Studies have reported increased probability of death to be associated with immobility (Ashwal, 2005; Cohen et al., 2008), lack of feeding skills, genetic

aetiology, hearing deficit (Cohen et al., 2008), inter-current illnesses with three or more co-existing disabilities (Decouflé and Autry, 2002), functional disability (Hutton, 1994), inability to recognise voices or speak intelligible words and incontinence (Katz, 2003). More recently, the presence of ventilatory airway support, pain/distress associated with feeding, and difficulty maintaining sitting position have been proposed as 'vulnerability factors' indicative of warranting palliative care (Harrop and Brombley, 2012) but the methods have not been reported in any detail. The focus of this review is mobility, a measurable aspect of body functioning allowing comparison; the International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2012) considers mobility to include a range of movements such as changing or maintaining a body position or location, carrying, moving or handling objects, walking or moving and using assorted forms of transportation.

The impetus behind prognosis research in children with impairments, includes planning for future care needs, health insurance (Katz, 2003; Strauss et al., 2000; Christakis and Iwashyna, 1998) and clinical decision making (Hayden et al., 2013). More recently, attempts have been made to further identify children with an increased risk of death for provision of palliative care services (Harrop and Edwards, 2013; Hain et al., 2013). Since access to palliative care is limited by an

uncertain prognosis, children with severe impairments may not have their needs fully met.

Rational

Knowledge of specific impairments of body functioning associated with increased likelihood of death in children can improve identification of those who may benefit from integrated palliative care.

Objectives

The primary objective for this review was to identify the likelihood of death associated with impaired mobility, in children with severe impairments, living in high income countries. This was done through a systematic review of studies reporting a point estimate of Hazard Ratio (HR) and Relative Risk (RR) for specific impairments of functioning related to mobility.

Method

Studies were retrieved using Medline, Embase, Cochrane Library, OpenGrey and Science Citation Index, from 1990 to 2016 and reference lists. Relevant studies

were located by combining search terms which included child, p?ediatric, disabilities, mortality, death, survival. For Medline search strategy see supplementary information. The last search was performed on 01/12/16. The reference lists of included studies, and the grey literature, were explored to locate potentially relevant studies for inclusion. No published protocol of the present review exists.

All retrieved papers were reviewed to include studies using the following criteria 1) observational cohort study with >50% follow up after 1980, published after 1990 2) majority of participants were children (<18) for most of the study 3) children described as having disability/impairments 4) studies relating to mobility 5) country of study defined by World Bank as high income, and, finally, 6) studies reporting a hazard ratio (HR) or relative risk (RR) for mortality. Studies of cancer, gestation, psychiatry, seizures, trauma, interventions, medicinal products, and the neonatal period were excluded, as were studies of prognostic factors unrelated to body functioning, such as biomarkers. As the focus of this review is prognostic factors, which are distinct from the actual cause of death, studies dealing with this alone, were also excluded.

All data were extracted onto piloted forms (SN) and then checked independently (EP).   The point estimates and associated confidence intervals of the hazard ratio (HR) and relative risk (RR) were abstracted for synthesis by two authors independently (SN, EP). Two authors (SN, EP) then independently assessed the quality of studies using the Quality in Prognosis Studies (QUIPS) tool (Hayden et al., 2013) which assesses quality in terms of study participation, attrition, prognostic factor and outcome measurement, confounding, statistical analysis and reporting, resulting in a judgment of high, moderate or low risk of bias. The forest plot was drawn in the R package 'forestplot'.

Results

Nine studies met the inclusion criteria (Figure 1, supplementary information). Data was extracted for impairments of body functioning related to mobility; most studies reported multiple factors. Figure 2 presents the findings in a Forest Plot, with immobility described as per study. This shows an indication of the magnitude of risk associated with each impairment but they are not necessarily directly comparable. The majority of studies reported functioning assessed using non-standardised measures; two studies reported the Gross Motor Function

Classification Scale (GMFCS) (Palisano et al., 2008) level V, (Westbom et al., 2011; Touyama et al., 2013); one study reported GMFCS combining level IV and V. (Baird et al., 2011)

The characteristics of included studies are displayed in Table 1. The risk of bias of included studies was judged using the QUIPS checklist. Of the nine papers included, four were judged to be at low risk of bias in all sections of QUIPS checklist (see supplementary information), the remaining studies had at least one section rated as moderate risk of bias. The most common aspect causing risk of bias was statistical analysis.

Seven papers were reported as retrospective cohort studies (Baird et al., 2011; Touyama et al., 2013; Hemming et al., 2005; Strauss et al., 1998a; Evans et al., 1990; Nielsen et al., 2002; Strauss et al., 1998b), one as case control (Cohen et al., 2008) (with two comparison groups) and one retrospective study of prospectively collected data (initial recruitment for another study, reporting vital status at a later point) (Westbom et al., 2011). This study suggested the data were collected as part of a research project, the remaining studies used routinely collected clinical data.

Studies used existing datasets, with two using the Client Development Evaluation Report (CDER) (Strauss et al., 1998a; Strauss et al., 1998b), two using registers of cerebral palsy (Westbom et al., 2011; Nielsen et al., 2002) and the remaining five, using clinical records, were reported as retrospective cohort studies (Baird et al., 2011; Touyama et al., 2013; Hemming et al., 2005; Evans et al., 1990; Cohen et al., 2008). Sample sizes ranged from 277 to 12,719 but were not consistently reported. All but two studies reported children with cerebral palsy as their population, one reported children as having 'developmental disabilities' and one with traumatic brain injury. Two studies originated in the USA, three studies originated in the UK, and singular studies were identified from Japan, Denmark, Sweden and Israel. Eight were published in English and one in Danish (translated by a native speaker). Three studies used the GMFCS (Palisano et al., 2008), although this scale categorises functioning rather than measuring it. Otherwise the measurement of functioning was unique to each study (or as in the case of the CDER, a local measure forming part of the data collection). Aspects of impairment, as potential prognostic factors, are presented as described by the study. In most cases the referent groups constituted those children who did not have the impairment or the degree of impairment differed, leading to a high degree of clinical heterogeneity.

Figure 2 shows that the singular factor associated with the highest ratio was 'lack of sitting ability at 24 months' with HR 44.4 (CI. 6.1 to 320.8) (Baird et al., 2011), however, sitting ability is defined as 'getting to any sitting position from any lying position on the floor and then sitting without propping with either arm for 15 seconds'. This equated to 56 out of 200 in the exposed group compared to 1 out of 132 children in the referent group. Two studies reported HR for GMFCS level V, with comparable results: 16.3 (CI 5.6 to 47.2), constituting 29 out of 166 children in the exposed group compared to 4 out of 413 in the referent group and 11.4 (CI 3.76 to 35.57) which equated to 25 out of 102 children in the exposed group compared to 5 out of 605 in the referent group (Touyama et al., 2013; Westbom et al., 2011). One study combined GMFCS level IV and V with a reduced HR of 6.2 (CI 2.8 to 14) equating to 55 out of 176 children in the exposed group compared to 2 out of 160 (Baird et al., 2011). In contrast, seemingly less severe impairments such as 'no functional hand use' and 'rolls/sits but cannot walk unaided' (Strauss et al., 1998a) were associated with lower hazard ratios of less than 3.

All studies reported a range of follow up times according to date of birth and end point of the study (Table 1) therefore it is not possible to make any meaningful judgments about the effect of length of follow up on the hazard.

Discussion

As far as we are aware, this is the first systematic review examining the impact of immobility on likelihood of death in children with severe impairments. We have extracted hazard ratios, which give an instantaneous risk at any given point over a period of time, and relative risk, which gives cumulative risk over a period of time. While only a small number of studies were identified, this review adds to the growing body of literature seeking to identify children most at risk of death, and who might benefit from palliative care. These findings suggest an association with increased likelihood of death, rather than prediction of death or imminent death, for which more data would be required. However, the findings have implications for practice, policy and research.

The clear majority of studies focussed on cerebral palsy, often seen to be a static condition. However, children may, in reality, have an unpredictable illness

trajectory. The clinical signs and level of disability for CP, for example, may change over time due to the long-term existence of hypertonia, contractures and musculoskeletal deformity, bone density, and life expectancy may be influenced by the presence of scoliosis, seizures, cardiac or respiratory factors (Wimalasundera & Stevenson, 2016). For the static conditions captured within this review, impairments to functioning are an early indicator of risk.

Given the increased likelihood of death for children who are not able to sit or 'cruise' at 24 months of age ('cruising' refers to walking while holding onto something, defined in the study as 'along furniture or wall, even if placed in standing, for at least two steps sideways in either direction') (Baird et al., 2011) and those in the GMFCS level V category, health care professionals should consider these as specific high risk factors for mortality. Nevertheless, all reported impairments were associated with an increased risk.

With regards to the assessment of functioning itself, its measurement was diverse and study specific. Gross motor function was assessed using the GMFCS, CDER or non-standardised measures based on clinical judgement. Notably, GMFCS category V is directly related to immobility, with consideration of head and truck control, but where this was not used, immobility was gauged in ways unique to

each study, which renders further statistical analysis problematic. Evans et al (1990) defined immobility as 'confined to a wheelchair which they did not propel themselves'; Cohen et al. (2008) defined immobility as 'no mobility'; Hemming et al. (2005) defined immobility as 'unable to walk even with aids, uses a wheelchair or is bed ridden'. Strauss et al. (1998a) uses 'rolls/sits but cannot walk unaided' and Strauss et al. (1998b) rates immobility by the lowest of five CDER items (rolling and sitting, hand use, arm use, ability to creep and crawl and ambulation). Nielsen et al. (2002) described immobility as 'ingen gangfunktion', translated into English as 'no walking function'. The GMFCS is considered a gold standard for categorising gross motor function and classifies into 5 levels. A more detailed measurement of gross motor function, such as the GMFM (CanChild, 2015) a 66-item scale, could potentially give more comprehensive information by measuring changes in functioning, but would require more resources. This measure would also define immobility more specifically and includes ability to roll and head control.

Hand use was categorised as no functional use as opposed to some functional use by Strauss (1998a), and by Baird et al. (2011) using a 4 point hand manipulation scale. For hand use, validated measures of functioning exist such as the Manual Ability Classification Scale (MACS) (Eliasson et al., 2006). For

more detailed assessment of hand and arm use, the QUEST (DeMatteo et al., 1993) or the Melbourne (Randall et al., 2001) are available.

The findings of this review suggest that immobility (however measured or categorised) is a potential prognostic factor. However, it is uncertain if this is specific to the populations studied, which is primarily children with cerebral palsy. The direct links between immobility and causes of death have not been examined in this review. Causes of death, such as respiratory infections (Sidebotham et al., 2014; Rousseau et al., 2015) may be due to factors such as immune insufficiency, poor swallowing, and inability to cough or achieve full lung expansion. This review only offers a reminder that children who are immobile are more at risk of death, and that palliative care provision should be considered. Research is needed to determine the links between immobility and causes of death, as immobility is unlikely to be a single prognostic factor but comprise of multiple impairments, making it at best a broad surrogate for these.

For consideration of likelihood of risk, accurate functional measurement is imperative, and we would recommend that the minimum level of functional assessment should include GMFCS and MACS with consideration given to the

more detailed assessments suggested above. With accuracy of functional measurement, changes in body functioning can also be monitored.

In the context of this review, the overall quality of the body of evidence was defined using the GRADE definition that is the extent to which we can be confident that these results reflect the association between prognostic factors and death in the underlying population (Huguet et al., 2013). Generalisability of these results to diagnosis other than cerebral palsy is limited, given all but two studies were conducted in this population. More specifically, according to GRADE (Huguet et al., 2013) the quality of a body of evidence involves a number of aspects. Consideration of within-study risk of bias (methodological quality) was judged to be moderate; the directness of evidence was judged to have no serious limitations as the samples were similar to the population of interest, although not necessarily to the broader population of children requiring palliative care. Although no formal tests of heterogeneity were undertaken, it was clear that there was heterogeneity of patient populations and in some cases between outcomes. Furthermore many of the confidence intervals are very wide, suggesting imprecise estimates of the population parameter.

However many of the effect estimates were strong, exceeding the GRADE levels of >2 and >5 for upgrading evidence by one and two levels respectively (GRADE, 2013). Given the existing limitations, the evidence would have been given an overall judgment of very low or low, had it not been for the high magnitude of effect associated with some results. Therefore, there is moderate quality evidence for GMFCS level V and immobility as being associated with an increased likelihood of death in children living in high income countries, and low quality evidence for head control and hand use. The small number of studies is of concern, this was due primarily to the requirement for HR or RR to be reported but we were unable to assess the risk of publication bias, which for prognosis research is a known issue (Huguet et al., 2013; Riley et al., 2014).

It is important to consider these findings alongside other available information, such as diagnosis (Hain, 2013). Communication of risk of death can support the difficult news of a potentially life limiting condition (Bluebond-Langner et al., 2016) which needs to be carefully discussed and considered alongside the individual preferences of the child and family for information (Andrews et al., 2013; Maltoni et al., 2005), with particular acknowledgement of the uncertainty reflected in the wide confidence intervals found in this analysis. However, if these factors are to

be used to inform provision of palliative care, there needs to be some consensus relating to the level of hazard indicative of the need.

Palliative care should be seen, not as an end-point, but as part of a broader health system. For example palliative care can be combined with rehabilitation approaches to facilitate self-management and self-care (Tiberini and Richardson, 2015), although this model is most commonly found in the adult literature (Oldervoll et al., 2011; Kelley et al., 2012). Palliative care as 'active total care' and rehabilitation are not, even for children, mutually exclusive. Integrating palliative care into existing service provision, tailored to the needs of the child and family, acknowledges the inherent uncertainty, while maximising the potential for health and wellbeing, alongside the risk that the child may deteriorate and die.

More rigorous research using prospective observational studies in defined populations, with validated measures of functioning are needed if we are to advance identification of children with increased likelihood of death, improve identification of life limiting conditions, and thus improve access to palliative care. However, such studies are likely to be costly, difficult to conduct and not able to report their findings for many years. New guidelines for reporting prognosis studies of tumour markers now exists (McShane et al., 2005), but none yet related

to functioning. Because of these problems, researchers should collaborate to develop a consensus about how to make better use of existing data, including the validated measures of functioning commonly used by health care professionals, particularly therapists, in this population of children.

Conclusions

This systematic literature review suggests that GMFCS level V and overall immobility are associated with a significantly increased likelihood of death in children, with existing severe impairments, living in high income countries. GMFCS can therefore support clinical judgement about whether integrated palliative care may be appropriate, as it provides a categorisation of immobility. In order to confirm this finding, researchers and health care professionals collecting routine data should use validated measures of functioning.

Declaration of conflicting interests

None

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