Economic Evaluations of Therapeutic Hypothermia Perinatal Hypoxic Ischaemic Encephalopathy

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Therapeutic hypothermia reduces the risk of death and neurological impairment in childrenwith hypoxic ischaemic encephalopathy. The article reviews the published literature examiningthe cost effectiveness of therapeutic hypothermia to treat neonatal encephalopathy.

Introduction

Neonatal encephalopathy is a major cause of death and neurodevelopmental impairment worldwide. New medical interventions are urgently needed to improve the survival and health outcomes of affected children. A recent meta-analysis suggests that reducing a child's body temperature 3-5°C below normal produces a statistically significant reduction in mortality and major neurodevelopmental disability at 18 months of age (risk ratio 0.81; 95% confidence interval [CI] 0.71-0.93) (Edwards et al. 2010). The cost of therapeutic hypothermia, however, is greater than standard care; it is thus important to evaluate the cost and health effectiveness trade-offs of this intervention before widespread implementation. This article begins by providing a brief overview of economic evaluation methods for informing healthcare management decisions, which is followed by a review of the clinical efficacy and cost effectiveness of therapeutic hypothermia to treat neonatal encephalopathy.

Economic Evaluation of Health Technologies

There are four main types of economic evaluation:
• cost-minimisation;
• cost effectiveness;
• cost-utility; and
• cost-benefit.

Each approach measures the cost of a health intervention in monetary units, but the methods differ with respect to characterising health outcomes. Cost-minimisation analysis assumes there is no difference in health outcomes and solely examines the cost implications of competing clinical management strategies.

Cost effectiveness analysis (CEA) characterises the health effectiveness of competing interventions in naturalistic units, such as the number of deaths prevented. The effectiveness outcome can also account for the duration of time spent in a health state. For example, the disability free life year (DFLY) statistic has been used in CEAs examining interventions in young children (Petrou et al. 2006). The primary outcome in CEA is typically the incremental cost effectiveness ratio (ICER), which has incremental cost (ΔC, Δ intervention minus standard care) in the numerator and the incremental effectiveness (ΔE) in the denominator.

Cost-utility analysis (CUA) values the effectiveness of the competing strategies using the microeconomic concept of utility, which can be valued using the standard gamble or time trade off techniques (Torrance et al. 1972), or via an 'off-theshelf' multi-attribute utility instrument (see, for example, Torrance et al. 1995). Utility weights are anchored on 0 (death) and 1 (perfect health), and health states worse than death are also possible. A widely applied summary effectiveness metric is the quality adjusted life year (QALY), which is calculated by multiplying the utility weight of a health state by the amount of time spent in that state. The primary endpoint in CUA is $\Delta C/\Delta QALY$.

The final approach is cost benefit analysis (CBA). CBA quantifies both costs and consequences in monetary terms. Estimating the value of a health effectiveness gain in monetary units can be achieved directly using contingent valuation techniques or by monetising benefit using respondents' preferences for alternative courses of action using conjoint analysis (see, for example, Regier et al. 2010 a). The primary outcome of CBA is net-benefit: Incremental cost subtracted from incremental benefit.

Regardless of approach, it is recommended that the statistical uncertainty surrounding each input parameter and primary outcome is reported (Briggs et al. 2006). When applying decision-analytic modelling techniques, a popular method to estimate confidence intervals (CIs) is to assign each parameter an empirical distribution; Monte Carlo simulation techniques are then used to propagate parameter uncertainty throughout the model (Briggs et al. 2006). The Monte Carlo replications provide incremental cost and effect pairs that inform 95% CI around primary outcomes and decision uncertainty. Decision uncertainty is communicated using the cost effectiveness acceptability curve (CEAC), which cumulatively plots the percentage of ICER draws that are cost effective at different thresholds of willingness to pay for an effectiveness gain (van Hout et al. 1994).

Efficacy of Hypothermia for Neonatal Rescue

Four large randomised controlled trials (RCTs) characterise the efficacy of therapeutic hypothermia for perinatal asphyxial encephalopathy. The CoolCap RCT (Gluckman et al. 2005) examined intensive care and selective head cooling for 72 hours (n=116) against intensive care alone (n=118). The primary outcome was severe disability or mortality. The former was defined as one of: gross motor function classification score (GMFCS) between 3-5, Bayley mental development index score of (MDI)<70 or bilateral cortical visual impairment at 18 months of age. The reduction in the risk of mortality and disability in the cooling arm was 0.61 (95% CI 0.34- 1.09). The NICHD RCT (Shankaran et al. 2005) studied intensive care plus total body cooling for 72 hours (n=102) or intensive care without cooling (n=106). The primary outcome was death or moderate-severe disability, where moderate disability was defined as having one of: MDI 70 to 84, GMFCS of 2, hearing deficit with amplification or a seizure disorder; severe disability was defined as: <70 on the Bayley MDI, GMFCS 3-5, or bilateral blindness or deafness at 18 months of age. The NICHD showed a statistically significant reduction in death or disability in the cooling arm (risk ratio 0.72, 95% CI 0.54-0.95). TOBY (Azzopardi et al. 2009) randomised encephalopathic infants to either intensive care plus total body cooling for 72 hours (n=163) or intensive care alone (n=162). The primary outcome was the combined 18-month outcome of mortality or severe neurodevelopmental disability defined as: MDI<70, GMFCS 3-5, or bilateral cortical visual impairment with no useful vision. The relative risk reduction in the cooling arm was 0.86 (95% CI 0.68 -1.07). A recently published RCT, the ICE trial (Jacobs et al. 2011), examined whole body cooling (n=110) against standard care (n=111) in tertiary and non-tertiary care centres. The primary outcome was death or sensorineural disability at 2 years of age defined as: Cerebral palsy, GMFCS 2-5, MDI<70, Bayley psychomotor development index score (PDI) <70, Bayley motor composite index score of <70, Bayley cognitive scale score <70, Bayley languages composite scale score <70, or blindness or deafness. The risk ratio for death or disability in the cooling arm was 0.77 [95% CI 0.62-0.98].

Cost Effectiveness Models of Neonatal Therapeutic Hypothermia

Two studies (Gray et al. 2008; Regier et al. 2010 b) have quantified the economic implications of therapeutic hypothermia for neonatal encephalopathy. Gray et al. (2008) examined the lifetime cost and utility differences of selective head cooling (SHC) for multiple scenarios that differed on the availability of abnormal amplitude integrated EEG (aEEG) screening or SHC. Each centre was defined by the level of care they could provide as defined by the American Academy of Paediatrics (Stark 2004). Clinical outcomes were obtained from the CoolCap RCT, and an ad hoc health state utility value of 0.67 was used if the child had neurodevelopmental impairment. If an infant had neurodevelopmental impairment, it was assumed they continued in that state throughout their life. Costs and longterm mortality rates were obtained from secondary data sources. A lifetime time horizon was used in the model. The primary outcome was ΔC/ΔQALY. Costs were reported in 2006 US dollars. Monte Carlo simulation for selected inputs was employed to characterise statistical uncertainty.

In the UK setting, Regier et al. (2010 b) used decision analytic modelling to synthesise clinical outcomes on mortality and morbidity from the TOBY, NICHD and CoolCap trials. Resource utilisation was directly obtained from prospectively collected data in the TOBY trial, which obviated the need to model the ability of a centre to offer aEEG or cooling. Three health states were modelled: Survival without neurological abnormality, survival with neurological abnormality, or death. Survival without neurological abnormality was defined as MDI>84, PDI>84, no neuromotor impairment, normal vision and hearing.

The primary outcome of the economic evaluation was the ΔC/ΔDFLY. The DFLY endpoint was calculated such that children without neurological abnormality were assigned a health state value of 1 for each disability-free year of survival (and 0 otherwise). The time horizon of the baseline model was the first 18 months after birth. In sensitivity analyses, the time horizon was extended to 18 years and children could transition between neurodevelopmental health states (Mangham et al. 2009). Costs and effects were discounted at a rate of 3.5% per year and were valued at 2006-2007 prices. Probabilistic sensitivity analysis using Monte Carlo simulation techniques was conducted.

• Measurement and Valuation of Resource Utilisation and Costs

Gray et al. (2008) obtained information on resource utilisation and costs from published literature and administrative databases. This limited their evaluation because the model was unable to discriminate neonatal length of stay by level of ICU care. Unit costs were obtained using cost-to-charge ratios calculated from Medicare and Medicaid Services Hospital Cost reports. The costs of acquiring the cooling equipment and the aEEG machine were obtained using market prices. These costs were amortised over 5 years and were distributed evenly across cooled infants. The indirect long-term costs of developmental impairment were incorporated via the costs associated with cerebral palsy as published by US Centre for Disease Control and Prevention (CDC 2004). Societal costs associated with productivity losses from premature mortality or inability to work were included, as were the costs of special education and out-of-pocket expenses for caregivers.

Regier et al. (2010 b) benefited from resource utilisation data collected alongside TOBY. This included micro-level information on the personnel required during transport to/from a cooling hospital, and the personnel required throughout the hospital stay. Further, the number of days in each level of neonatal care as defined by the British Association of Perinatal Medicine (BAPM 1992) was reported, as was the estimates on hospital readmissions, outpatient hospital visits, and the use of other healthcare services at 6, 12, and 18 months post initial discharge. Unit costs were attached to resource utilisation using data from the National Health Service Reference Costs database and the British National Formulary. The market costs of acquiring the aEEG machine and the total body cooling system were annuitised over 5 years. The non-capital variable costs of

cooling were informed via telephone interviews. The cost of aEEG and cooling were incorporated into the model by dividing the equivalent annual cost of the machines by the number of infants per year that received cooling in the TOBY RCT centres. Societal costs were not included in the model.

• Results from the Economic Models

Gray et al. (2008) reported that cooling resulted in lower lifetime costs and greater QALYs in each of the scenarios examined. The degree of cost savings and QALYs gained differed little between the assumed scenarios. The average cost in the usual care arm was US $2,133 per birth and was between $2,066 and $2,084 per birth in the SHC scenarios. The estimated mean cost savings in the cooling strategy ranged from $49 to $67; the QALYs gained in each scenario were between 0.0066 and 0.0088. The authors did not report 95% CI's, but the percentage of ΔC and $\Delta QALY$ replications that were jointly cost saving and more effective was between 68% and 73%, depending on the scenario. The percentage of ICERs that were expected to be below a willingness to pay threshold of $50,000 per QALY ranged between 88% and 92%.

The economic model by Regier et al. (2010 b) found that cooling resulted in an incremental cost of (UK) £3,787 (95% CI: - 2,516-12,360) in the first 18 months after birth. The percentage of Monte Carlo replications that resulted in expected cost savings was 15%. For effectiveness, cooling resulted in a statistically significant DFLY gain of 0.19 (95% CI: 0.07-0.31). The ICER was £19,931 per DFLY gained in the baseline analysis. The CEAC suggested the probability of cost effectiveness was 69% at a willingness to pay for a DFLY gain of £30,000. The scenario analyses found that when the time horizon of the model was extended to 18 years, the incremental cost was £1,847 (95% CI: -4,494-10,303) and the incremental effectiveness was 1.30 DFLYs gained (95% CI: 0.51-2.15). There was a 99% probability that cooling is cost effective when at a willingness to pay threshold of £20,000.

Conclusion

New, expensive technologies have propelled the expenditure of scarce healthcare resources into the spotlight over the past 40 years. Adopting interventions that 'bend the cost curve' and improve health outcomes is the new mantra, and decision makers are thus increasingly turning to healthcare economic evaluation to inform optimal management strategies. The economic cost and consequences of therapeutic hypothermia to treat perinatal asphyxial encephalopathy has been examined from the UK and US perspectives; the evidence surrounding the cost effectiveness of therapeutic hypothermia is uncertain over the short-term, but seems favourable when a longer-term perspective is adopted.

In the UK, Regier et al. (2010 b) state that the cost effectiveness of therapeutic hypothermia is 'finely balanced' when the analysis is restricted to 18 months after birth. Their conservative conclusion was influenced by the considerable decision uncertainty surrounding the cost and effects of therapeutic hypothermia over the short term. Over the medium and long-term, both Gray et al. (2008) and Regier et al. (2010 b) find that therapeutic hypothermia is likely to be cost effective at acceptable willingness to pay thresholds. Gray et al. (2008) further predicted that the majority of the cost replications were jointly cost saving and more effective, irrespective of the scenario examined.

Conclusions surrounding the cost effectiveness of therapeutic hypothermia over the medium- and long-term should be treated with caution because the data used to project outcomes beyond the RCTs was not prospectively collected for that purpose. Long-term panel data examining the long-term costs, effectiveness, and change in demand for cooling services should be prospectively collected to better inform the likely economic impact of therapeutic hypothermia. Nonetheless, existing cost effectiveness models can, in part, inform local decisions on the likely economic impact of implementation, and current evidence suggests that therapeutic hypothermia is likely to be cost effective and may result in reduced costs and better health outcomes for encephalopathic infants over the long-term.

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