The value of evidence: a re-analysis of the use of steroids in head injury

Retrospective case study: the CRASH trial

Susan C. Griffin, Claire McKenna and Karl Claxton, Centre for Health Economics, University of York, UK

PURPOSE

The value of clinical research lies in improving treatment decisions to improve health. Research proposals need to demonstrate this value to obtain funding. Funding is limited and so there is a need to prioritise among potentially valuable research designs.

We aimed to show how formal, quantitative assessments of cost-effectiveness and the value of further evidence can improve the process of research prioritisation by identifying research designs that offer the greatest improvement in health.

THE CASE STUDY

Decision problem (in 2000)

Should public funds be used to investigate the effect of steroids for treating severe traumatic brain injury?

Disease burden

- 10-20 severe TBI per 100,000 population
- Leaving approx 1 in 3 dead and 1 in 3 disabled

Intervention

- Cheap, generic, no private sponsor
- Variable use in practice (12-64% of ICUs)
- Uncertain effectiveness

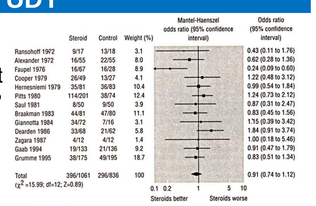


Fig 1 Summary odds ratio for death at end of study

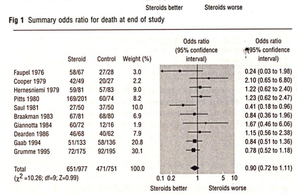


Fig 2 Summary odds ratio for death or disability at end of study

From Alderson P, Roberts I. Corticosteroids in acute traumatic brain injury: systematic review of randomised controlled trials. British Medical Journal. 1997;314:1855-59.

RE-ANALYSIS OF CASE STUDY

Limiting consideration to the RCT evidence on death only does not provide a complete evaluation of the cost of uncertainty.

Additional relevant evidence

- Clinical outcomes other than death, as measured by Glasgow Outcome Scale (GOS):

  Death, persistent vegetative state, severe disability, moderately disability, recovered
- Health related quality of life and life expectancy conditional on GOS
- Health service resource use conditional on GOS:

  Opportunity cost of increased resource use

  Displacement of other health-generating activities

Decision analytic model

Specifies logical mathematical relationship between multiple sources of evidence

Probabilistic analysis reflects joint impact of uncertainty from all sources of evidence

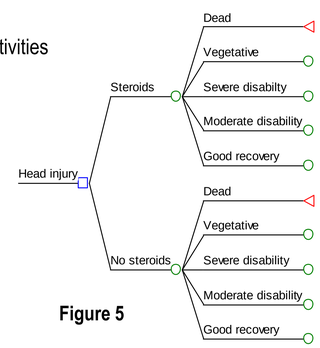


Figure 5

VALUE OF EVIDENCE

Is more evidence valuable?

Compare health gains with decision based on current evidence to one with reduced overall uncertainty

- Answer is yes: additional evidence could prevent forgoing of potential health gains from steroids

What type of evidence is required?

Examine contribution of each input parameter to overall uncertainty

- Answer is more information on the numbers left dead, vegetative or severely disabled would reduce decision uncertainty
- More information on health related quality of life, life expectancy or resource use would not be valuable as would not reduce decision uncertainty

How much evidence is required?

Compare costs of research study to value of expected reduction in decision uncertainty

- Benefits of CRASH trial design recruiting 20,000 patients expected to exceed cost
- Smaller study could have achieved same value of reduction in decision uncertainty
- Assuming that trial leads to perfect implementation

What is required to change clinical practice?

Need some assessment of factors that influence clinicians' decisions

- Size of CRASH trial and unexpected results ensured high profile
- Would other means to change practice represent better value for money?

Should research be prioritised?

Compare the net health gains of proposed research studies

Requires that alternative proposals be compared on same basis

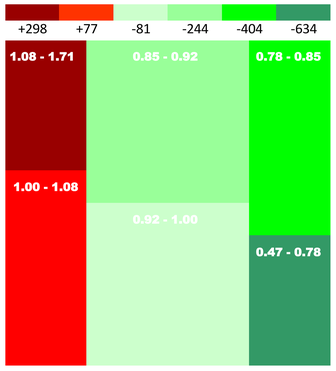
Graphical illustrations of uncertainty in the effect of steroids compared to no steroids

Treemaps based on random effects meta-analysis of mortality reported in 16 trials (1975-1995).

Area of coloured square shows probability of odds ratio (OR) falling within range specified.

Colour of square indicates annual number of deaths following TBI relative to no steroid use.

Figure 3. The cost of uncertainty: number of deaths annually in the UK

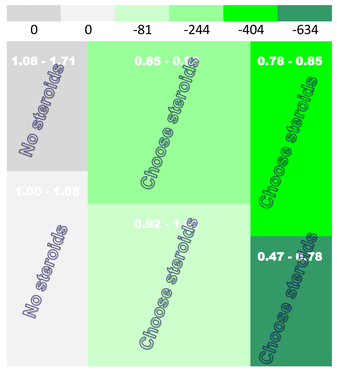


Decision based on current evidence

- Choose steroids as expect reduction in deaths
- Risk that true OR exceeds one and deaths increased compared to no steroids
- Error probability ~25%

On average expect to prevent 175 deaths per year if provide steroids based on current evidence

Figure 4. The value of evidence



Decision after further research

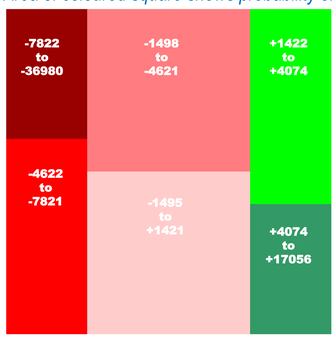
- Further research reduces uncertainty about true value of OR
- Choose steroids only if OR less than one
- Avoid risk that deaths increased
- Expect greater health gains as a result

On average expect to prevent 217 deaths per year if can choose to provide steroids only if they are life saving

RESULTS

Figure 6. Uncertainty in the effect of steroids on number of TBI patient years lived in full health annually in the UK

Area of coloured square shows probability of healthy years lived falling within range specified.

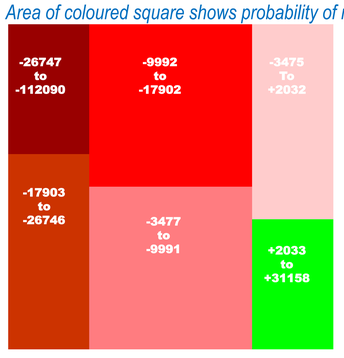


Incorporating impact on health related quality of life and life expectancy changes optimal decision based on current evidence because steroids associated with increased risk of vegetative state or severely disability

- Don't choose steroids as expect reduction in number of health years lived for TBI sufferers
- Risk that true QALY gain is positive compared to no steroids
- Error probability ~25%

Figure 7. Uncertainty in the effect of steroids on number of person years lived in full health annually in the UK

Area of coloured square shows probability of net health benefits falling within range specified.



Incorporating impact on health service resource use shows that steroids would increase costs and displace other health-generating activities

- Don't choose steroids as expect reduction in number of health years lived overall in UK
- Risk that true health gain is positive compared to no steroids
- Error probability ~10%

DISCUSSION

Despite the potential to aid decisions about the use of research resources, formal methods of economic evaluation are not widely used. This contrasts with the increasing use of economic evaluation in reimbursement decisions. The discrepancy may be due to the separation of institutions with the remit for making reimbursement decisions from those responsible for commissioning research even though the objectives underlying both policy decisions are the same, i.e. to improve overall population health.

Using cost-effectiveness analysis to estimate the impact of research designs on overall health adds value to the research prioritisation process by enabling:

(i) comparison of all competing proposals on the same basis;

(ii) efficient, transparent and accountable allocation of funds;

(iii) optimisation of research design to ensure that further evidence directly addresses decision uncertainty.

Limitations:

- Requires development of cost-effectiveness analysis at research proposal stage rather than reimbursement assessment
- Formal methods may not capture all things of interest (e.g. value of establishing network of researchers in reducing costs of future trials)

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