Treatment for severe head injury

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SUMMARY Difficulties in establishing the value of certain treatments for head injury are reviewed. An analysis of 1000 severely head injured patients, managed by varying methods in three different countries, showed that certain treatments were more often used in the most severely injured patients. Even when the severity of injury was taken account of, it appeared that the use of steroids and tracheostomy did not affect outcome; but that patients undergoing mechanical ventilation had outcomes which were worse than expected. The value of treatments proposed for severe head injury needs rigorous scrutiny.

"As soon as a new, but still unproved, method of treatment is adopted by even a minority of the medical profession, it becomes virtually impossible to conduct the controlled trial that alone can furnish truly reliable evaluation of its effectiveness and its hazards."¹

This comment by a British neurologist applies with particular force to therapy for severe head injuries. Whilst the risk that *new drugs* will do more harm than good have diminished because of recent statutory restrictions on widespread adoption before adequate trials, there are no limits to the application of therapeutic methods which involve surgical procedures, mechanical ventilation and various regimens of drugs already in common use.

The last 20 years have seen the adoption of a number of therapeutic techniques designed to control events which threaten life after severe head injury. In 1958 a dramatic reduction in mortality was attributed to the introduction of what would now be called respiratory intensive care (tracheostomy and suction).² A decade later controlled ventilation was reported to have further improved outcome.³ Corticosteroids have been widely used for many years, in spite of a lack of specific evidence for their value; there are recent reports that a very large dose improves outcome.⁴ Claims for the value of large bony decompressions have been made,^{5,6} and

retracted.⁷ Several years ago there was a vogue for using hypothermia to reduce cerebral metabolism, but this is now seldom used. There have been recent reports,^{8,9} that the use of large doses of barbiturates may be beneficial for these patients.

In spite of all these efforts Langfitt¹⁰ recently concluded that there had been little change in mortality from severe head injury over the last 50 years; but he drew attention to the recent reports of Becker *et al*¹¹ and of Bruce *et al*,¹² which he considered did indicate an improvement in outcome; to these has been added the series of Marshall *et al*.^{8,13} However, there has been considerable discussion about the validity of the claims for these methods, which are very demanding of personnel, time and facilities.

There are several reasons why it is difficult to establish the efficacy of treatment for severe head injury; these can be conveniently grouped as practical, ethical and statistical problems. Among *practical* problems are that treatment regimens usually include several components (for example surgery, controlled ventilation, osmotics, steroids and other drugs); and that decisions about the initiation of therapy have to be made rapidly. Because of the need for rapid decision-making there is little time to evaluate the degree of brain damage and to estimate accurately what the prognosis would be without the particular therapeutic modality under consideration. In trials of therapy for many other conditions there is time for analysis of data about an individual patient, and for discussion

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between members of therapeutic teams and trial coordinators about which combination of methods to use in a particular case.

An *ethical* problem is perceived by many clinicians because of the high mortality rate of this condition, and of its predominant occurrence in young patients. This might be regarded as emotional rather than ethical—but it is a fact that doctors faced with this condition frequently consider that every possible measure must be used which might assist recovery, even if the efficacy of some of these methods is unproven. Doubts about the ethics of controlled trials for conditions associated with a high mortality have recently been expressed.^{14 15}

The *statistical* problems are not unique to this condition. However, several of the circumstances that create difficulties in proving the efficacy of therapy in any branch of medicine tend to occur together after severe head injury, and these combine to frustrate attempts to reach a satisfactory conclusion. To begin with, the definition of severity depends crucially on when, where and by whom assessment is made, as well as on the criteria adopted. Moreover, any method of treatment will have a proportion of “successes”, and a considerable difference in outcome will be needed before a statistically significant change is detected. Considering the number of variables which can influence outcome, large numbers of patients must be studied before a significant effect is likely to be evident from the application of alternative treatments to sets of similar cases.

In spite of the prevalence of head injury, only a fraction of patients admitted to hospital are severe—and these tend to be widely dispersed. Only the largest services can accumulate a sizeable series of patients, and few of these admit many more than 50 patients a year. For a result to be obtained within a reasonable time period, multicentre data collection is therefore required, with all the difficulties which this entails.

International Data Bank Study

It seemed to us that unless outcome could be predicted reliably, in at least a proportion of identifiable patients, it was unlikely that the influence of alternative forms of management on outcome could be detected. This led us to initiate a systematic approach to this problem, with the intention of evolving standardised ways of assessing initial severity and ultimate outcome after severe head injury, so that the relationship between these two could be explored, as a basis for prediction. This study began in Glasgow 12 years ago, and later acquired data also from the Netherlands and Los

Angeles. Data collection and analysis are still proceeding, but already it has proved possible to predict outcome in many individual patients on the basis of clinical data available during the first week after injury.¹⁶ Although methods of assessment were strictly standardised in this data bank there was no attempt to impose uniform treatment regimens on the collecting centres, but the methods used were always recorded. In the event there were marked differences between the three countries in the relative frequency with which various therapeutic measures were used. This makes it possible to make some observations about the effects of certain forms of treatment on outcome.

Patients studied

These were collected prospectively from Glasgow (since 1968), from Rotterdam and Groningen (since 1972) and from Los Angeles (since 1974) using standardised methods of assessment and recording. Details of the collecting centres, of the indicators of severity used, and of the features of the first 1000 patients, have been published.¹⁵ The present analysis of treatment methods is based on 1250 patients, collected between 1968 and 1977 inclusive; 118 patients treated during 1968 and 1969 in Glasgow, which were included in previous published papers, were treated before the Glasgow neurosurgical unit moved into the city from its country location at Killearn, are excluded from the analysis in this paper. Patient selection was by one criterion only—the persistence of coma for more than 6 hours. Coma was defined as not opening the eyes at all, not obeying commands and not uttering any words.

Indicators of severity

From analysis of the relationship between clinical features in the first week and the outcome 6 months after injury we were able to identify indicators of severity.¹⁷ Features which were associated with a worse outcome indicated a more severe injury, and these included depth of coma, nonreacting pupils, impairment of spontaneous and reflex eye movements, and abnormal patterns of movement in the limbs. One of the most useful single indicators of severity is the state of responsiveness on the Glasgow Coma Scale^{18 19}; this can be summarised by the coma score or sum, made up by adding the scores on each of the three components to give a figure which ranges from 3 (deepest coma) to 15. As described elsewhere²⁰ this provides a less accurate indicator of severity than does the exact composition of the score—but nonetheless it is a useful means of comparing approximate severity, and is now widely

Table 1 Severity and age in three countries in different years

	Glasgow 531	Netherlands 302	LA 224
Coma Sum 3-5*			
70-71	25%		
72-73	21%	40%	
74-75	20%	42%	24%
76-77	31%	26%	29%
Average 70-77	25%	36%	27%
Non-reacting pupils*			
70-71	16%		
72-73	17%	17%	
74-75	15%	31%	29%
76-77	26%	21%	28%
Average 70-77	19%	26%	29%
Age < 20 years			
70-71	60%		
72-73	37%	47%	
74-75	33%	40%	19%
76-77	27%	41%	21%
Average 70-77	36%	41%	20%
Intracranial haematoma			
70-71	42%		
72-73	52%	26%	
74-75	59%	36%	62%
76-77	57%	35%	50%
Average 70-77	54%	34%	56%

*Best state in first 24 hours

used in reports of head injured patients. Age is also significantly related to outcome.²¹

Patients in three countries

Although these patients were all of similar minimum severity (coma at least 6 hours), there were differences among the three countries in the proportion of patients with various features (table 1). Another difference was that fewer patients were admitted to the neuro-service within 6 hours of injury in Glasgow. There was relatively little change in the characteristics of the patients from year to year during the period in any one centre of data collection.

The outcome 6 months after injury was very similar in each country, both for the series as a whole and for subsets matched for various features (table 2). Again there was little change during the years of data collection.

Different therapeutic measures

The management of severely head injured patients, some of them with multiple injuries, is a complex affair, and it is particularly difficult to compare overall standards of care. We chose to compare the frequency with which six separate components of therapy were used and to study the relationship between their use and outcome. The modalities were those about the value of which there is current controversy, or at least doubt.

Table 2 % Dead/vegetative at 6 months in different countries and years

	Glasgow	Netherlands	LA
All cases			
70-71	43%		
72-73	46%	47%	
74-75	44%	52%	53%
76-77	51%	46%	54%
Average 70-77	46%	50%	54%
With intracranial haematoma			
70-71	52%		
72-73	50%	50%	
74-75	51%	54%	61%
76-77	57%	66%	72%
Average 70-77	53%	58%	66%
No haematoma			
< 72	32%		
72-73	41%	48%	
74-75	34%	48%	39%
76-77	43%	31%	36%
Average 70-77	37%	42%	37%

1 Steroids were given as dexamethazone 4 mg 6 hourly or its equivalent. Treatment was started on the first day after injury in 86% of those cases in which it was employed, but the exact interval between injury and commencement within this period was not recorded. Treatment was continued in survivors for several days in decreasing doses. A minority of patients with pulmonary complications received lower doses of steroids, and have not been included in the steroid treated group. No patients in the present analysis received "mega-dose" steroids.⁴
2 Osmotics consisted of one or more doses of mannitol, usually a 20% solution over 10-30 minutes to a total dose varying from 0.3 g/kg to 1.0 g/kg. The indication for giving mannitol was often the demonstration of a high level of intracranial pressure during continuous monitoring. There were, however, other patients in whom the indications were empirical; patients awaiting surgery for intracranial haematoma sometimes received mannitol, and it was continued postoperatively when brain swelling had been noted at the end of operation. Sometimes the indication was deterioration in a patient's clinical state, irrespective of whether the patient had a haematoma.

Decompressive craniectomy

It was not the practice in any centre to employ large deliberate decompressions by hemicraniectomy,⁶ circumferential craniotomy⁵ or bifrontal craniotomy. The usual method for dealing with an acute intracranial haematoma was by a generous fronto-temporal craniotomy. The bone flap was sometimes left out in patients whose brain appeared swollen at the end of operation.

Endotracheal tube and tracheostomy

Tracheostomy was usually performed when it was evident that there was likely to be a prolonged need for endotracheal intubation; it was rarely done within the first day or two of injury unless there were associated facial or chest injuries. Differences in the rate of intubation in the three centres partly reflects variations in the reliance upon this measure as a means of ensuring an adequate airway and gas exchange, but is also related to the more frequent employment of assisted ventilation in two of the centres.

Mechanical ventilation

The cases classified in this group did not include those in whom ventilation was used only terminally in fatal cases, nor those in whom mechanical assistance was triggered by the patient. Respiratory insufficiency was usually the indication for controlled mechanical ventilation, but in some cases the purpose was to provide the brain with the supposed benefits of hypocapnia.³

Frequency of use of different treatments

When the three countries were compared there was for each of the six therapeutic techniques one country which differed in its use of it, as compared with the other two countries; each country was equally often the "odd one out" (table 3). During the period of data collection there were changes in the frequency with which some methods were used in Glasgow (for which the period of study is longest).

Table 3 Treatment in three countries (1970–1977)

	Glasgow 531	Netherlands 302	L A 224
Steroids	24%	34%	99%
Osmotics—No haematoma	28%	19%	28%
Haematoma	53%	31%	64%
Bone flap out (% of craniotomies)	28%	92%	93%
Tracheostomy (any time)	10%	15%	66%
Mechanical ventilation	18%	28%	13%
ET tube or tracheostomy (first 3 days)	38%	61%	70%

Table 4 Treatment over 8 years (531 cases in Glasgow)

Years	Steroids	Tracheostomy	Dead/Veg at 6 months
70–71	52%	23%	43%
72–73	26%	9%	46%
74–75	20%	6%	44%
76–77	15%	8%	51%

Table 5 Therapy and outcome (all centres (70–77), all coma scores)

Therapy	Without this therapy		With this therapy	
	n	%D/VS	n	%D/VS
Steroids	588	49	447	51
Osmotics	651	43	386	60
Bone flap removal (% of craniotomies)	190	44	185	67
Tracheostomy (ever)	811	48	248	51
ET/tracheostomy (first 3 days)	410	30	649	61
Mechanical ventilation	732	40	327	68

Steroids are now less frequently used, as is tracheostomy; but more patients are intubated in the first 3 days and there is a small increase in the use of controlled ventilation (table 4); there were no significant difference in outcome associated with these changes in treatment.

Treatment and outcome

When patients who did or did not receive various kinds of treatment were compared as a whole there was no evidence of a better outcome in the treated group; where there was a difference the treated patients had a higher mortality. It seemed that this might reflect the tendency noticeable in all three countries, for each of these therapies to be used more often for patients who were more severely affected. Therefore it was considered important to make allowance for the severity of brain damage when comparing the outcome of patients who did, with those who did not, receive each of these various treatments.

Patients were therefore divided into three grades of severity on the basis of the best state on the Coma Scale in the first 24 hours, and comparisons then made between those who did or did not receive each treatment modality within these severity grades. In the most severely affected patients there was little difference between treated and untreated patients, both having a high mortality (table 6). In the other

Table 6 Severity of injury, therapy and outcome at 6 months

Coma sum 24 hour best	% Dead or vegetative	
	Steroids	No steroids
3/5	77%	82%
6/7	47%	48%
> 8	20%	23%
All levels	50%	50%
	Tracheostomy	No tracheostomy
3/5	72%	83%
6/7	45%	47%
> 8	39%	22%
All levels	53%	48%

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Table 7 Effect of therapy on outcome (stratifying for age, coma sum, pupils, haematoma, country)

Therapy	Number of deaths			
	Without this therapy		With therapy	
	Expected	Observed	Expected	Observed
Steroids	232.4	232	193.6	194
Ventilation	274.9	249	152.1	178
Tracheostomy	320.2	319	106.8	108

patients outcomes were *less* good in the treated patients, except for those treated with steroids; no difference could be found between patients who did or did not have steroids. This might suggest that the coma sum was an inadequate means of matching patients, and that other factors might be associated both with a poor outcome and with a tendency to attract more intensive treatment. A further analysis was therefore undertaken which allowed not only for coma sum but also for pupil reaction, the presence of intracranial haematoma, the patient's age and the country in which he was treated.

The statistical technique used was based on that described by Peto and Pike,²² and previously used by one of us.²³ First the data were divided into *n* strata, a stratum being one combination of levels of each relevant variable. Within each stratum the treatment was divided into different groups, ie airway management was divided into 3 groups. Group 1 had endotracheal intubation; group 2 had tracheostomy and group 3 had neither. If *O_j* and *S_j* represent respectively the number of survivors observed and the total number studied in group *j*, the expected number of survivors, *E_j*, can be computed assuming mortality independent of treatment group. From this the deviation *D_j*=*O_j*-*E_j* was calculated and summed over all strata. These total deviations (which sum identically to zero) were then tested for significant departure from the null hypothesis by taking the quadratic form $\chi^2 = dA^{-1}d$ to be asymptotically distributed as chi-squared on *m*-1 degrees of freedom, where *d* is the vector formed by the first *m*-1 total deviations (*m* = total number of groups for the treatment), and *A* is their covariance matrix, the formula for which is given by Peto and Pike.²² When this analysis was done there was usually no difference in outcome between treated and untreated patients; when there was a difference, again the outcome was *less* good in the treated groups.

Discussion

The patients reported here were all managed in well equipped and well staffed specialised centres, and the fact that many of these severely affected patients

survived and became independent reflects the benefit of this treatment. Given this good general management, however, it seems from this study that certain components of therapy, which are commonly used in intensive care units, do not markedly affect the outcome in patients who are brain damaged enough to be in coma for 6 hours or more. It is interesting that we should have reached this conclusion about steroids, using our method of comparison, when two recent controlled trials have also shown that steroids do not have an effect—even in high doses.^{24 25} This suggests that our conclusions about other measures may also be valid. The study did not (directly) investigate the importance of the interval after injury (within the first day after injury) at which treatment was started. We have elsewhere emphasised the importance of measures designed to prevent secondary brain damage which may lead to coma of the duration which qualified patients for inclusion in the present study.^{26 27}

Whenever outcome proves to be *similar* in groups of patients who have received different treatment, three interpretations are possible:

- 1 the treatments are not effective in influencing outcome;
- 2 treatment is effective only if instituted soon enough, or
- 3 only for some types of patient (of a certain age group, or with particular kinds or grades of severity of injury).

In that event the beneficial effect may be obscured by failure to take sufficient account of the interval before treatment, or of certain features of the patients. For example, this study confirms that there is a group of patients so severely affected that the outcome is uniformly bad, regardless of treatment; there is also evidence that the most severely affected patients tend to be the most intensively treated. However, we have carried out analyses which allow for various severity factors, for age, and for whether or not neurosurgical care began within 6 hours; we were still unable to demonstrate a beneficial effect for the measures under consideration.

When the outcome is *better* in one group of patients than another, several explanations are possible:

- 1 the treatment of one group has been more effective. Most regimens used after severe head injury comprise several modalities and it may be difficult to discern which component is in fact contributing to an improved result.
- 2 specialised care (in general) has been started sooner after injury in the patients with a better outcome, and it is this rather than particular components of treatment which accounts for the better outcome.

3 assessment of initial severity or of outcome, or both, has not been well enough standardised between the two patient populations being compared. The importance of rigorous attention to the standardisation of methods of assessment cannot be over-emphasised. The comparisons in this paper are based upon data collected prospectively according to methods which were carefully agreed and standardised in advance; this was not always the case in some studies with which the results of this data bank have been compared. The minimum criteria of coma for 6 hours applied in this study seems not to have been met in all cases in other series. Moreover, in one study¹¹ observations were originally made according to a different system for assessing responsiveness, but the patients were re-analysed retrospectively in an attempt to apply the criteria of the data bank. 4 Other factors have not been sufficiently carefully matched in the groups of patients under analysis. These include features known to influence outcome, such as the age distribution of the series, and hidden variables, not yet recognised as affecting outcome, and therefore not taken into account. Thus the comparison between the series of children mean age 7 years reported by Bruce *et al*¹² and the data bank (mean age 33 years) is invalid. Likewise the series reported by Marshall *et al*¹³ from San Diego was unusual in that 75% of patients with high intracranial pressure did *not* have a haematoma. In most other centres raised intracranial pressure is usually a sequel of the damage associated with an intracranial haematoma.

5 Statistical factors may account for the appearance of improved outcome—which is in fact not significant. The commonest reason for this is inadequate sample size; but the distribution in the two populations of various features which affect outcome may also be crucial even though there appears to be comparability by simpler measure of similarity. Those various factors are discussed elsewhere.^{20 21 30}

Another approach to investigating the efficacy of different therapies is to use the methods currently being evolved for predicting outcome on the basis of data available soon after injury.^{21 28} An effective treatment would be one that led to a “better than predicted” outcome in a significant number of patients, when predictions were based on a training set of patients not treated by the method under examination. Such an analysis has not yet been completed for all the treatment methods discussed in this paper.

In a quarter of patients in the data bank it becomes clear at an early stage that they will do well with conventional intensive management; another quarter are obviously destined to die because of brain

damage so severe that survival is inconceivable, no matter what management is applied. Prediction of outcome soon after injury would make it possible to recognise these patients, and attention could then be focussed on those whose outcome was in doubt, and therefore liable to be influenced. In this way the efficacy of a particular therapeutic technique would likely be detected much more rapidly because its benefit would not be submerged or obscured by its use in many patients whose outcome was already determined.

Treatment of severe head injury is not the only form of intensive therapy about which there is current controversy about efficacy. Colleagues studying patients in coma due to nontraumatic lesions found no better outcome in those who had been more intensively investigated and treated.²⁹ Recent comments on the paucity of evidence for the effectiveness of special coronary units in reducing mortality from myocardial infarction might be considered to apply also to claims about certain regimens for severely head injured patients. One editorial³¹ concludes “We should no longer accept sweeping claims for a substantial reduction of mortality, since hard-won experience tells us that a true reduction of this magnitude is very unlikely to be produced so readily. The apparent mortality rate of patients admitted to a coronary care unit can be altered drastically by minor variations in the age structure, infarct-timing, and general health of the patients. Claims for a major alteration in mortality cannot therefore be accepted without an assurance that like is being compared with like.”

As new methods are devised and introduced, the supposed benefits of each need to be subject to rigorous scrutiny and analysis, according to agreed methods of assessment. We should obey Pasteur’s injunction to “keep your enthusiasm but let strict verification be its constant companion.”

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