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Mortality amongst multiple trauma patients admitted to an intensive therapy unit

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KEYWORDS
Anasthetic techniques; sedation, intravenous • *Trauma*; intensive care

ABSTRACT

A retrospective review of 428 severely injured patients admitted to an intensive therapy unit between 1969 and 1982 was performed. The patients' primary injuries were assessed using the injury severity score (ISS), and subsequent complications using the complications impact index and sepsis score. Between 1969 and 1980 mortality fluctuated between 19% and 29% but rose to 47% ($p < 0.05$) during 1981–82 in spite of an unchanged ISS. The increased mortality was confined to ventilated patients surviving more than 5 days from injury and was associated with multiple organ failure and severe infection. The rapid and sustained increase in mortality could not be explained by any obvious change in severity of injury or referral pattern. The only deliberate change in management related to the combination of analgesic sedative drugs used in ventilated patients. During 1979 to 1982 mortality was 28% in patients given morphine with or without benzodiazepines and 77% in those given morphine and etomidate ($p < 0.0005$). After discontinuation of the latter regimen (May 1983) and resumption of the former analgesic/sedative combination, mortality fell to 25% ($p < 0.005$). Possible mechanisms leading to increased mortality include adrenocortical insufficiency or depth of anaesthesia.

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Summary

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Key words

Anaesthetic techniques; sedation, intravenous.
Trauma; intensive care.

A retrospective review of severely injured patients admitted to an intensive therapy unit (ITU) between 1969 and 1982 was carried out to identify reasons for an apparent increase in mortality during the period 1981–1982. The influence of intensive care on the relationship between the severity of injury and outcome, although not extensively studied, has been shown to be beneficial.[1,2] An apparent increase in mortality therefore demanded explanation. Preliminary reports of our findings were presented at the Second European meeting on Intensive Care[3] and later published.[4] The present paper contains the definitive data from the original retrospective study together with some additional prospective results.

A requirement of any study involving evaluation of the management of patients suffering from multiple trauma is an objective means of describing the severity of injury and its relation

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to outcome. One such clinical scoring system, based on the abbreviated injury scale,[5] is the injury severity score (ISS) which has been shown to relate closely to outcome.[6] This relationship has been validated by a number of independent authors.[7–9]

The ISS formed the basis for comparing the initial severity of injury throughout the 14-year study period. Two additional scoring systems were used to assess subsequent complications, including infection, in a detailed analysis of the four year period from 1979 to 1982.

Patients and methods

The admission and discharge records of a busy general ITU were examined to obtain the number of multiple trauma patients admitted between 1969 and 1982 and their outcome. From these records it was possible to confirm that mortality in 1981–1982 had increased.

The age, sex and ISS of patients admitted between 1969 and 1978 were obtained from computer records. Detailed clinical data for patients admitted between 1979 and 1982 were obtained directly from the case notes. The clinical, radiological and operative data available for determination of an accurate ISS were more than adequate. A score of 0–5 was assigned to the injuries in each of five body areas according to the abbreviated injury scale.[5] The three highest scores were squared and summed to obtain the ISS. As a means of assessing subsequent complications including infection, the complications impact index[10] and sepsis score[11] were determined at 24 hours after admission to the ITU. The sepsis score was re-assessed 24 hours prior to death or discharge from the unit.

By 1979 the pattern of care of these patients had become well established.[12] Initial resuscitation consisted of restoration of intravascular volume and cardiac output by the infusion of colloid and crystalloid. Filtered and warmed blood and blood products were transfused as indicated to maintain a haematocrit of 30–35% and to correct coagulation defects. Failure to restore blood volume and cardiac output by the above means prompted the early use of agents such as inotropes and/or vasodilators. Indications for mechanical ventilation were failure of adequate oxygenation (arterial oxygen tension (Pao_2) < 65 mmHg breathing 15 litre/min oxygen through a high flow mask), excessive respiratory effort, ventilatory inadequacy with hypercapnia or coincidental head injury. Intra-arterial, central venous and urinary catheters were used in all patients to monitor cardiovascular and respiratory status. A small number of patients with complex haemodynamic problems required balloon tipped flow-directed pulmonary artery catheters for monitoring of pulmonary artery and pulmonary capillary wedge pressures. Patients with significant head injuries were transferred to the Institute of Neurological Sciences.

Although the policy of the unit is not to use prophylactic antibiotics routinely in patients with multiple trauma, the high incidence of referred patients in this series resulted in variability of initial antibiotic administration. Subsequent antibiotic therapy was dictated by bacteriological surveillance. Any change in antibiotic usage was on the basis of probable clinical superiority over existing agents and on expert bacteriological advice. In-line bacteriological filters, tunnelling of central lines and three-litre feeding bags were used with increasing frequency during the period of study. Parenteral (or occasionally enteral) nutrition was commenced immediately following initial resuscitation and maintained throughout the period of stay in the ITU. Antacids and H_2 receptor antagonists were not administered routinely but only when gastrointestinal bleeding occurred or in the presence of renal failure.

During the period 1979 and 1982 the only deliberate changes in management policy related to the use of analgesic and sedative drugs and steroids. During 1979 and 1980 patients requiring ventilation received opiates (morphine or, rarely, phenoperidine) either in bolus doses or by continuous intravenous infusion with (46%) or without benzodiazepines by intermittent injection. In 1981 a number of patients were similarly managed but during this year a short acting hypnotic drug (etomidate) given by intravenous infusion, was gradually introduced and by 1982 all patients requiring ventilation received morphine and etomidate by infusion. Etomidate was administered in a dose sufficient to maintain sleep,[13] more or less uninterruptedly, until weaning from mechanical ventilation was considered feasible.

Towards the end of 1981 the occurrence of an Addisonian crisis in a patient who was critically ill and septic following severe multiple trauma prompted the measurement of serum cortisol by radioimmunoassay in all patients subsequently

admitted to the unit.[14] Some of these latter patients received replacement doses of hydrocortisone.[14,15]

Statistical analysis of the data was performed using a χ^2 test with Yates correction, a value of $p < 0.05$ being taken to indicate significance.

Additional data

Following completion of the above analysis, etomidate was discontinued in May 1983, since when 16 patients with multiple trauma were treated in the unit, of whom 12 were ventilated and survived more than 5 days. The policy for the use of sedative and analgesic drugs in these patients had reverted to that existing prior to the introduction of etomidate by infusion. Daily serum cortisol assays were obtained in all 12 patients.

Results

During the period 1969 to 1982 a total of 428 patients were admitted for treatment of multiple trauma. Between 1969 and 1980 (Fig. 1) mortality fluctuated between 19% and 29% but rose to 47% ($p < 0.05$) during 1981 to 1982. There was no statistically significant change in ISS throughout the entire period (20–26).

Subsequent detailed analysis of the data between 1979 and 1982 revealed that the pattern of referral and mortality during 1979 to 1980 was similar to the preceding 10 years (Table 1). A comparison was therefore made between this period and 1981–1982, which had the advantage of minimising the influence of any change in the pattern of treatment. Seven patients were unsuitable for inclusion on the grounds of inadequate notes or because of penetrating injuries (four in 1979/80, three in 1981/82).

During 1981–1982 there was an increase in the number of patients referred to the unit (Table 2) but no change in the mean age, ISS, pattern of referral or proportion of patients receiving mechanical ventilation. Early mortality (< 5 days from injury) was also unchanged. The increased mortality therefore was confined to patients surviving more than 5 days from the time of injury. All these patients received mechanical ventilation.

On further detailed examination of the ventilated patients surviving more than 5 days (Table 3) mortality rose from 23% to 61% but, as before, no statistically significant difference was observed in any of the measured factors felt to influence mortality. The only obvious difference between the two groups related to the regimen used to provide analgesia and sedation. When the patients were grouped according to the two forms of sedation during the whole four-year perod (Table 4), a clear difference in mortality (28% in the group given opiates with or without benzodiazepines and 77% in the group given opiates and etomidate) was revealed. The shorter

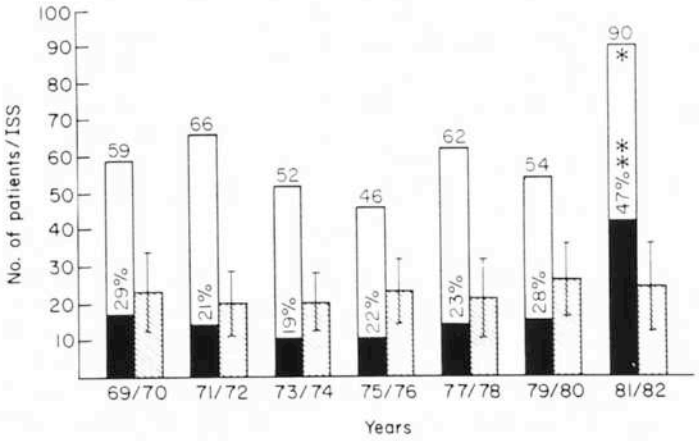

Fig. 1. Mean (SD) mortality (■) and injury severity score (□) amongst multiple trauma patients admitted to an ITU between 1969 and 1982. An increase in rate of referral and mortality occurred during 1981/82 whilst ISS remained unchanged. *$p < 0.005$, **$p < 0.05$.

Table 1. Comparison of the periods 1979/80 and 1969/78.

	1979/80	1969/78	Significance
Number of patients	54	285	
Male:female	2.1:1	2.8:1	NS
Mean (SD) age, years	41 (21)	45 (17)	NS
Mean (SD) injury severity score	26 (10)	21 (10)	NS
Mortality	28%	23%	NS

NS = not significant.

Table 2. Comparison of selected 2-year study periods

	1979/80	1981/82	Significance
Patients	54	90	
Male:female	2.1:1	2.1:1	NS
Age			
Range (years)	11–88	13–76	
Mean (SD)	41 (21)	34 (17)	NS
Injury severity score			
Range	9–45	4–57	
Mean (SD)	26 (10)	24 (12)	NS
Referral < 24 hours	39 (71%)	55 (62%)	NS
Mechanically ventilated	41 (76%)	62 (68%)	NS
Mortality	15 (28%)	42 (47%)	$p < 0.05$
Died < 5 days from injury	7 (13%)	12 (13%)	NS
Died > 5 days from injury	8 (15%)	30 (33%)	$p < 0.025$

NS = not significant.

Table 3. Comparison of patients surviving more than 5 days

	1979/80	1981/82	Significance
Number of patients	30	47	
Mortality	7 (23%)	28 (61%)	$p < 0.005$
Mean (SD) age, years	40 (20)	34 (15)	NS
Referral < 24 hours	8 (26%)	20 (42%)	NS
Injury severity score			
Range	9–41	9–57	
Mean (SD)	28 (10)	28 (9)	NS
Sepsis score			
Range	4–19	2–19	NS
Mean (SD)	10 (4)	10 (3)	
Complications impact index			
Range	13–54	26–46	
Mean (SD)	38 (9)	36 (6)	NS

time to death in the latter group did not reach statistical significance. Further sub-division on the basis of ISS indicated higher mortality in the morphine and etomidate group at all severities of injury (ISS 10–20, 2/15 vs 4/6, $p = 0.06$; ISS 21–30, 4/13 vs 5/9, $p = 0.5$; ISS > 30 8/22 vs 12/12 $p < 0.005$). A similar pattern was observed in the relationship between mortality and complications impact index.

The mode of death in the two groups of ventilated patients was similar—multiple organ failure in association with severe infection. In addition to respiratory failure (100%) the incidence of renal and hepatic failure amongst non-survivors was 74% and 29% respectively. The early and late plots of sepsis score (Fig. 2) indicate the association between mortality and severe infection in both groups of patients. Four percent

Table 4. Comparison of patients receiving two forms of sedation

	Morphine and/or benzodiazepine	Morphine and etomidate	Significance
Number of patients	50	27	
Mortality	14 (28%)	21 (77%)	$p < 0.0005$
Mean (SD) time to death, days	20 (9)	14 (14)	NS
Mean (SD) age, years	36 (18)	35 (15)	NS
Referral < 24 hours	19 (38%)	10 (37%)	NS
External referral	31 (62%)	19 (70%)	NS
Injury severity score			
Range	9–57	13–41	
Mean (SD)	27 (10)	27 (8)	NS
Sepsis score			
Range	2–19	6–16	
Mean (SD)	10 (4)	10 (2)	NS
Complications impact index			
Range	13–54	23–47	
Mean (SD)	37 (8)	34 (8)	NS

NS = not significant.

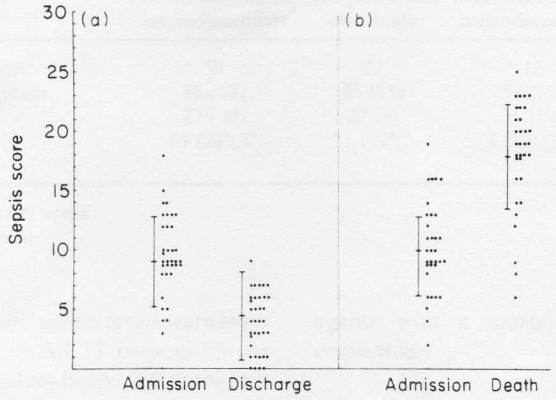

Fig. 2. Sepsis scores (including mean and SD) in (a) survivors and (b) non-survivors of the group of patients ventilated for more than 5 days. Mortality was consistently associated with major sepsis, (a) $p < 0.05$, (b) $p < 0.005$.

of the morphine/benzodiazepine and 15% of the morphine/etomidate groups had positive blood cultures at some stage of their illness; the spectrum of organisms between the two groups was indistinguishable, and patients became increasingly infected with the passage of time and with the onset of multiple organ failure. There was no obvious outbreak of nosocomial infection during the 4-year period of detailed study.

With respect to the dosage of analgesic and sedative agents (Table 5), the group given morphine with or without benzodiazepines received an equivalent daily dose of morphine to that in the group given morphine and etomidate. In the former group, 24 of 50 patients received morphine by bolus dose only, with a mean (SD) of 64 (36) mg/24 hr ($p < 0.05$). However, in the latter group given morphine by infusion only, 10 of 27 patients received comparable low doses of morphine. No relationship was found between the dose of either of the drug regimens and mortality.

Serum cortisol measurements were made in 17 of 27 patients in the morphine and etomidate group. None of the patients in the group receiving benzodiazepines had cortisol measurements. Pre-

Table 5. Mean (SD) dose (mg/24 hours) and duration (days) drugs used for sedation and analgesia

	Morphine and/or benzodiazepines	Morphine and etomidate	Significance
Morphine			
Dose	117 (66)	120 (82)	NS
Duration	7 (6)	10 (9)	NS
Benzodiazepine			
Dose	20 (10)	—	—
Duration	3 (2)	—	—
Etomidate			
Dose	—	787 (417)	—
Duration	—	9 (7)	—
Pancuronium			
Duration	6 (3)	9 (8)	NS

NS = not significant.

Table 6. Mortality after discontinuation of etomidate

	Retrospective study		Prospective study	
	Morphine and/or benzodiazepines	Morphine and etomidate	Morphine and/or benzodiazepines	Significance
Number of patients	50	27	12	
Mean (SD) age, years	36 (18)	35 (15)	37 (15)	NS
Mean (SD) ISS	27 (10)	27 (8)	31 (10)	NS
Mortality	14 (28%)*	21 (77%)	3 (25%)**	*$p < 0.0005$ **$p < 0.01$

ISS = injury severity score.
NS = not significant.

viously accepted 'normal' serum levels were from 260 to 550 nmol/litre.[14] All 17 patients in the etomidate group had values below 260 nmol/litre on at least one occasion. Ten patients had at least one value below 100 nmol/litre; several on consecutive days. There was a clear temporal relationship between the administration of etomidate and the low cortisol values. Eight patients, of whom four died, received replacement doses of hydrocortisone.

Finally, while 10 of the 50 patients in the morphine/benzodiazepine group received an intropic drug (dopamine) 22 of 27 in the morphine/etomidate group required similar treatment (dopamine, adrenaline and isoprenaline, $p < 0.0001$). In the former group inotropic drugs were first required 9.5 (SD 7.6) days and in the latter group 3.4 (SD 3.2) days, from the day of admission; this difference was not statistically significant. Eleven patients in the morphine/benzodiazepine group and eight in the morphine/etomidate group received H_2 receptor blocking agents with a mortality of 54% and 100% respectively.

Additional data

Of the 12 patients with multiple trauma treated since discontinuation of etomidate, three died (Table 6). Thus the mortality has returned to the level prior to the introduction of etomidate by infusion. Of more than 170 estimations of serum cortisol, none was below 260 nmol/litre and 132 exceeded 550 nmol/litre.

Discussion

Retrospective analyses of hospital case records are inevitably vulnerable to criticism. Nevertheless, if mortality rate is at issue and the difference in mortality between groups of patients is substantial, careful evaluation of all the relevant factors is mandatory. The strengths of the present evaluation are the comprehensive and detailed nature of the ITU case records and the diagnostic

certainty of multiple trauma—in this case exclusively blunt trauma without significant head injuries. The marked increase in mortality rate could therefore be detected at a relatively early stage and attention was directed toward the change in sedation regimens. The conclusions could have been more convincing had the two regimens been in use concurrently (thus reducing the possible influence of other factors)—a clear lesson for the future.

Examination of the ISS revealed that prior to the period 1981/82, mortality in this centre was somewhat higher than that reported from some other centres.[7–9] The difference, however, was not great and could be attributed to the high incidence of referred cases (with attendant delay in definitive treatment) in the present series. The rapid and sustained increase in mortality in 1981/82 was without precedent and could not be explained by any obvious change in severity of injury or referral pattern—the increase in the number of patients during this period represented a progressive increase in both external and internal referrals. Careful examination of unit procedure during the 4-year period revealed no consistent change which might reasonably account for an increase in mortality. This included such important issues as levels of staffing in relation to overall workload. In spite of increasingly strict measures to counter infection, the mode of death in both groups of patients was multiple organ failure associated almost invariably with intractable sepsis. A similar mode of death was recently described in 88% of patients dying of blunt trauma in a Dutch centre.[16]

The only deliberate change in management policy was the combination of analgesic and sedative drugs used in ventilated patients. Etomidate was initially introduced to facilitate the care of patients whose acceptance of mechanical ventilation using morphine and benzodiazepines was poor, but ultimately, all ventilated patients received both morphine and etomidate. The practice of maintaining such patients 'well sedated and detached from the ITU environment' gradually gained favour – in line with 67% of British intensive therapy units included in a recent survey.[13] The possibly unusual aspect of this change of practice was that etomidate was used virtually to the exclusion of alternative agents such as Althesin. Furthermore, whilst benzodiazepines were rarely used for more than 2 or 3 days and then in less than half the patients, etomidate was administered systematically throughout the period of mechanical ventilation and the daily dose of morphine remained unaltered.

It is difficult to eliminate the probable contribution to increased mortality of the change in analgesic/sedative regimen. Morphine would not appear to be an important factor since both regimens contained comparable daily morphine dosage. The increased mortality in the morphine/etomidate group of critically ill patients would, therefore, be attributable to etomidate, a possible interaction between morphine and etomidate or a greater depth of 'anaesthesia' (possibly independent of the analgesic/sedative combination).

The mechanism whereby a change to morphine and etomidate might result in increased mortality must necessarily be speculative. There is now good evidence that etomidate by infusion inhibits basal cortisol production in the adrenal cortex and abolishes the stress response;[17–21] similar changes occur in aldosterone production.[22] These effects are due to inhibition of mitochondrial hydroxylation e.g. 11 β hydroxylation and 17 α hydroxylation.[22] Adverse effects on the cardiovascular system may ultimately result[23–25] and recent experimental[26,27] and clinical data[15,28] suggest a relationship between low blood cortisol and mortality in relation to stress; steroid administration has been reported to reduce mortality in cortisol-depleted, stressed animals and patients.[15,27,28] The fact that the patients in the present study did not die from acute adrenal insufficiency is hardly surprising given circumstances where careful monitoring and control of fluid and electrolyte balance are routinely performed together with the early use of inotropic agents. Sodium and fluid balance, in which disturbances have been reported in response to etomidate,[17] was not analysed in this study but both acute and long-term effects attributable to cardiovascular instability were observed as shown by the more frequent use of inotropic drugs in the morphine/etomidate group and the high incidence of renal failure. The longer term effects of adrenal insufficiency (or other possible actions of etomidate) on metabolic and vascular mechanisms (including capillary permeability) and superadded infection have not been investigated.[29]

The evidence relating the depth and duration of 'anaesthesia' to host defence response is sparse

and conflicting;[30] if the overall effect were to depress, an increased incidence of infection unresponsive to existing antibiotics would be a probable outcome. Thus the recent trend in some centres towards keeping critically ill patients asleep[13] may be undesirable.

The retrospective study has shown that the administration of etomidate by intravenous infusion was associated with increased mortality in critically ill, traumatised patients. Data obtained during the period of the prospective study support this association. Further laboratory investigations of this apparent effect would seem to be essential; in the meantime, maximum caution is advised if long-term infusion of any sedative agent is contemplated.

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Note added in proof

A recent clinical report (Wagner RL, White PF, Kan PB, Rosenthal HH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. *New England Journal of Medicine* 1984; **310;** 1415–21) has described prolonged depression of cortisol and aldosterone production after discontinuation of etomidate by intravenous infusion. The duration of infusion was 20 hours.