

Bispectral index and intensive care – an alluring concept

With a focus on health care resources, reviews of the utilities of existing medical interventions are commonplace. For new treatments and techniques we have a responsibility to conduct these reviews prior to a change in our standard practice. Discovering the limited utility of an alluring but expensive innovation after it is entrenched in practice, conjures up images of horses and unbolted stable doors. The history of medicine is littered with such examples.

Nowhere else is this issue more sharply focused than with health care providers, in an attempt to minimise interventions with little or no value. The following coverage criteria for interventions, for example, have been suggested: a) it should produce its intended effects on health outcome, b) its beneficial effects should outweigh its adverse effects, and c) it is the most cost effective method available compared with the best available alternatives.¹ It is hard to argue with such an apparently simple approach, although issues such as the cost-benefit analysis of expensive interventions with marginal benefits remain difficult.

In anaesthesia, a robust measurement of depth of anaesthesia is seen as the Holy Grail, and is clearly an attractive proposition. The output from the Bispectral Index (BIS) does not relate to any mechanistic effect of drugs, but to an observational relationship based on a very large number of clinical cases correlating clinical signs with EEG output. Not surprisingly, therefore, there is good evidence that the BIS tracks clinical signs of sedation/hypnosis with certain drugs.² In the light of these data, the Bispectral Index has potential utility in anaesthesia, especially considering the “user friendly” features in the design of the Aspect monitors. The limitations of BIS do, however, need to be recognised.

For example, the need to consider mentally recalibrating the BIS in the presence of N₂O and opioids,³ EMG interference and the effect of changing stimulus on BIS, all need to be considered. Furthermore, it should not be forgotten that BIS can be used only to predict the likelihood of a clinical state - absolute values may not protect against awareness.⁴

A large quantity of basic data on BIS now exists. The challenge today is to evaluate its utility in health care to ensure it represents appropriate use of health

care resources. We might consider this in relation to the criteria for health interventions outlined earlier. In terms of intended effects in anaesthesia, it does track the effect of some sedative/hypnotics reasonably well (the limitations above should be heeded). The criteria suggested by Eddy,¹ however, require that this translate into some outcome benefit – this might be reducing awareness risk or permitting lighter anaesthesia (better quality recovery, faster emergence/discharge, reduced drug usage).

The first benefit is not proven, but is being systematically addressed in a large randomized multi-centre trial in Australasia (The B-Aware Trial). The second benefit appears relatively minor.² In terms of beneficial vs adverse effects, the key consideration is the risk of increasing awareness by titrating to a BIS endpoint; this should also be addressed by the B-Aware Trial. In terms of cost-benefit, the financial burden is significant, at around 50 million dollars annually in Australia (disposables alone, with routine use in anaesthesia). This figure presumably would exceed half a billion dollars in the USA. In the face of such a cost, we would seem obliged to consider whether routine use represents an effective use of health care resources, once we have adequate data on its effect on outcome.

In intensive care, the potential benefits are similar - avoiding excessive sedation (faster recovery/discharge, less adverse haemodynamic effects, lower drug costs) and avoiding accidental undersedation. It must be noted, however, that there are a number of differences between the intensive care unit (ICU) setting and that used in the development of the BIS algorithms in anaesthetised subjects. This particularly relates to many of the sedative/analgesic dose regimens, the incidence of neurological impairment, and the potential for EMG artifact. Will this induce variability which limits its utility? The answer is we don't know. There are data demonstrating a relationship between BIS and sedation scores in intensive care which demonstrate considerable scatter,^{5,6} the data are relatively sparse, and there are limitations such as the lack of explicit detail on the dose regimens used. Nicholson *et al* in this issue of the journal use the BIS as an index of staging sleep in the ICU which is a novel application but which also has limitations.⁷

As stated previously, a key point in the assessment of the benefit of an intervention is whether or not it produces outcomes which are better than those achieved with current practice. It is important to note that, unlike in anaesthesia, some sort of “gold standard” of sedation exists for many of the patients in intensive care, namely patient responses and sedation scoring systems. While not perfect, these are essentially cost free, are more closely related to the goals of sedation than an EEG surrogate, and are easily performed in the large group of

ICU patients in whom deep sedation or paralysis is not required. Certainly, the situation is different when contact with the patient is lost, where the existing benchmark practice, as in anaesthesia, is clinical judgment.

The BIS may be of benefit in intensive care, and the concept is certainly alluring. There are, however, inadequate data on which to make a judgment about its utility. Prior to the widespread adoption of these monitors by intensive care units, we have a responsibility to perform studies which fully assess the relationship between BIS and clinical evidence of sedation, and, further, which seek to demonstrate whether it provides a true or perceived benefit.

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Blunt abdominal trauma - how should we investigate a "kick in the guts"?

The assessment and management of a patient with blunt abdominal trauma (BAT) is often difficult. This is even more so when BAT is associated with injury to

other areas of the body, which is often the case with trauma. History and examination in association with some laboratory tests are an essential part of the work-up, but are often nondiscriminatory in their own right. The issue of who needs a laparotomy, and who does not, is unclear and the number of investigations employed to help decide this indicate that none of them are specific. There seems to be agreement in the literature that if the patient is haemodynamically unstable then laparotomy is the investigation of choice, although what defines 'haemodynamic instability' is often unclear.

Nevertheless, the management of a haemodynamically stable patient with BAT is still a dilemma. There are six main techniques that have been used for its assessment. They are laparotomy, serial physical examinations, laparoscopy, CT scanning, ultrasonography and diagnostic peritoneal lavage (DPL). While attempts have been made to assess the value of each of these investigations in managing BAT and to determine the investigation of choice, currently no definitive answer is available.^{1,2} In the meantime it is useful to review the strengths and weaknesses of each.

Diagnostic laparotomy is still the investigation of choice in the 'unstable' patient. However, in the stable patient it has fallen out of favour due to complications associated with a negative laparotomy. There are many reports describing conservative management of an intra-abdominal injury especially injury to solid organs. However, it is often difficult to decide if the data presented indicates the ideal management or that which may have worked but which places the patient at an unacceptable risk when simply using a firm resolve 'not to operate'.

Serial abdominal examinations using the 'experienced hand' is a time honoured part of management. However, the presence of head injuries, sedative drugs or other distracting injuries renders this technique unreliable. Moreover, in Australasia, particularly after hours, the 'experienced hand' is often not 'on site' and therefore unable to perform the serial examinations. The main advantage of serial examinations is its simplicity. The main disadvantage is that a negative or equivocal examination does not rule out significant injury.

Abdominal CT scanning has been embraced enthusiastically by some as the investigation of choice for the suspect abdomen. Advantages include accurate images of solid organs and the ability to localise and sometimes quantify an intra-abdominal source of injury. Abdominal CT is also extremely useful in the paediatric patient with BAT. Disadvantages include the cost, time taken to perform the test and the need to shift the patient from a monitored to a nonmonitored area. Laparoscopy has been used as an investigation for BAT but in general it has been found to be of little value.

Ultrasonography has recently gained favour as a use-

ful technique for investigating BAT.³ Focussed abdominal sonography in trauma (FAST) is widely taught to emergency physicians and is reported to have excellent results.⁴ Its advantages include speed of application and its ability to be performed with ease in the resuscitation area. The disadvantages include a need to learn a new technique and the requirement to have an expensive machine immediately available. The results are also operator-dependent.

Diagnostic peritoneal lavage (DPL) has been recommended by the advanced trauma life support (ATLS) system since the late 1980s. Catre reviewed a large number of prospective studies of DPL and found a sensitivity and specificity of 98% and 92%, respectively.⁵ However, in the setting of pelvic fractures there can be a high false positive rate. Classic positive results for DPL include aspiration of frank blood on initial insertion, red blood cell counts > 100,000/ μ L, white blood cell counts > 500/ μ L and the presence of amylase, bile or vegetable matter. Advantages of DPL include the speed of application, its ability to be performed in the resuscitation room and its accuracy. Disadvantages include its invasive nature and the false positive rate, which appears variable in different reports. An added disadvantage includes the difficulty of interpreting the presence of free fluid in any subsequent abdominal CT scan.

The results of CT, ultrasonography and DPL provide different information and so an accurate comparison is not possible, although all purport to look for free fluid in the abdomen.

Blunt abdominal trauma with hollow viscus injury (HVI) is difficult to identify early as it may not be associated with significant bleeding and thus haemodynamic instability. Yet delays in operation are associated with an increased rate of infection with associated morbidity and mortality.⁶ Naggapan and Frank from Monash Medical Centre, elsewhere in this edition,⁷ provide a case report which considers the utility of the cell count ratio (CCR) from DPL as a diagnostic tool to detect HVI. They refer to a report from Fang *et al* who first described this method,⁸ and suggest, as Fang did, that the technique has a high diagnostic specificity.

Superficially it appears that the CCR could be very useful. However, in Fang's original paper the mean time from injury to DPL was 5 hours (range 1.5 to 18 hours) and from the Naggapan and Frank case report a period presumably in excess of 1 hour prior to DPL had occurred (which would seem likely as he underwent extensive resuscitation, ultrasonography and CT scanning prior to the DPL). While the data from Fang's study show an impressive sensitivity and specificity, one wonders whether the data would be as impressive were the time from DPL to injury much less, given the

nature of the cellular inflammatory response. It would be interesting to see if these data are reproducible for shorter time periods between injury and DPL.

In the meantime the various modalities described above will continue to be used by their relative devotees. Despite the mounting evidence supporting ultrasound and DPL, it seems likely that abdominal CT will also continue to be widely used. Time will tell whether the CCR also becomes a useful part of the armamentarium.

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Are there any evidence-based indications for the use of mannitol in acute tubular necrosis?

Currently, there are no agents that consistently demonstrate significant renal protection in the normotensive critically ill patient in whom an adverse renal

influence exists (e.g. sepsis, myoglobin, radio-contrast, NSAIDs, aminoglycosides). Nevertheless, mannitol, dopamine and frusemide are still used for prevention and/or treatment of acute tubular necrosis (ATN).¹ In this edition of the journal the renal protective effect of mannitol is once again under the spotlight and was found to be of no benefit in the setting of orthotopic liver transplantation.²

Mannitol is a non-absorbable, non-metabolisable carbohydrate with a molecular weight of 182. When it is administered intravenously as a hypertonic solution, the extracellular fluid volume increases due to a fluid shift from the intracellular to the extracellular compartments. With glomerular filtration, it remains within the nephron lumen causing an osmotic diuresis largely by inhibiting sodium and water transport in both the descending and ascending segments of the loop of Henle.³ Less than 50% of its action is due to inhibition of sodium and water reabsorption in the proximal tubule.³

In the experimental model of ATN it improves renal function,⁴⁻⁹ and was one of the first 'renal protection' agents used in clinical practice,¹⁰ being used in patients with haemoglobinuria or myoglobinuria,¹¹ and in patients who required amphotericin B,¹² cisplatin,¹³ abdominal aortic surgery,¹⁴ open heart surgery¹⁵ or surgery when jaundiced,¹⁶ in an attempt to reduce the incidence of ATN. It is also used to protect renal graft function during cadaveric kidney transplantation.^{17,18}

The 'renal protection' effect is thought to be due to its ability to increase nephron luminal flow and renal blood flow (due to renal vasodilation mediated indirectly by increased PGI₂ synthesis¹⁹), as well as its ability to reduce ischaemic cell swelling and act as a free-radical scavenger.²⁰ However, while there appears to be a protective effect in the presence of low renal perfusion pressures, the glomerular filtration rate remains unchanged or even diminishes in intact animals and normal individuals (i.e. with normal renal perfusion pressures) when mannitol is infused.²¹⁻²⁴

While the renal protective effect of mannitol may have been demonstrated experimentally, it has not been confirmed in clinical practice by prospective randomised controlled trials.^{25,26} For example, pretreatment with mannitol has not improved the postoperative renal outcome in jaundiced patients (it may even worsen renal function²⁷), mannitol does not protect against an acute deterioration in renal function in patients with chronic renal failure²⁸ or diabetes²⁹ who are given radiocontrast (it may also worsen renal function), and mannitol is of no benefit in patients undergoing aortic surgery.³⁰ Furthermore, mannitol is not without side effects, including exacerbation of cardiac failure³¹ ischaemic neuronal injury,³² hypotension,³³ factitious hyponatraemia,³⁴ hyperosmolality³⁴ and even acute renal failure.³⁵⁻³⁷

To the question 'Are there any evidence-based indications for the use of mannitol in acute tubular necrosis?' - the answer would currently seem to be 'No'. Maintaining normal renal perfusion and limiting the administration of nephrotoxic agents (e.g. NSAIDs, radiocontrast, aminoglycosides) still remain the essential principles for prevention and management of ATN in the critically ill patient.³⁸

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Osmotherapy in traumatic brain injury - overused and dangerous

Osmotically active agents such as mannitol, have been, and continue to be, widely used in the treatment of all neurological emergencies. This includes traumatic brain injury, subarachnoid haemorrhage and stroke. Their use is based on an often strongly held clinical belief that osmotherapy is integral to management of all causes of intracranial hypertension. Although this practice is predicated on a reasonable theoretical basis, the evidence for beneficial effects of these agents is lacking.¹

Theoretically, mannitol increases plasma osmolality causing a net efflux of fluid from areas of damaged oedematous brain, with resultant reduction in intracranial pressure. An intact blood brain barrier is necessary for this to occur. Other purported beneficial effects include reduction in cerebrospinal fluid formation and scavenging of potentially toxic free radicals.² However, these benefits have not been confirmed in clinical trials.

Following intravenous administration of mannitol, an immediate plasma expanding effect occurs that reduces haematocrit and alters red cell viscosity, temporarily increasing cerebral blood flow. Subsequent reductions in intracranial pressure probably result from restoration in cerebral perfusion pressure and rheological changes in cerebral blood flow, rather than specific cerebral dehydration.² This effect is more pronounced in situations where cerebral blood flow is compromised (e.g. within 72 hours following traumatic brain injury or subarachnoid haemorrhage).³

Osmotherapy is associated with a number of potentially adverse effects. Mannitol exerts an effective osmo-

tic effect over a narrow range of plasma osmolality (i.e. 290-330 mosmol/L) above which the theoretically beneficial effects may be negated. It will induce an osmolar gap which may be exacerbated by alcohol (which is frequently present in head injured patients) causing the plasma osmolality to increase to levels that may be above the upper therapeutic limit of 320 - 330 mosmol/L. As mannitol and alcohol are potent diuretics, the administration of a standard dose in intoxicated patients may rapidly induce a diuresis causing an hyperosmolar state. The combined effect may compromise systemic blood pressure, particularly if the patient is hypovolaemic, potentiating cerebral ischaemia (particularly during initial resuscitation of the head injured patient) and lead to an adverse outcome.^{4,5} Mannitol (and alcohol) induced diuresis may also be exacerbated by the concomitant administration of catecholamines which are used to defend systemic (and cerebral) blood pressure.

A strong pathophysiological argument can be made to explain the high risk vs benefit relationship when using mannitol indiscriminately in all patients with suspected intracranial hypertension. This reasoning may also provide a rationale for the lack of positive clinical trials of osmotherapy in these patients.

The Brain Trauma Foundation Guidelines for the management of severe head injury recommend mannitol as an option only in resuscitated patients with unequivocal signs of raised intracranial pressure prior to imaging or evacuation of a mass lesion.^{6,7} These recommendations do not apply to all patients with coma, yet mannitol is frequently administered to patients with non-traumatic causes of coma.

Although doses of mannitol are quoted as 0.25 -1.0 g/kg, lower doses are equally as effective in terms of improving cerebral perfusion and are associated with a lower incidence of side effects. In general terms, 20 mL of 20% mannitol will suffice, rather than the inappropriate 'reflex' 500mL bag that is often administered.⁸

Hypertonic saline (3% solution) exerts similar osmotic plasma expanding effects to mannitol. These solutions do not generate an osmolar gap so that plasma sodium reflects the true plasma osmolality thereby allowing easier titration. These solutions have been advocated as "small volume resuscitation fluids" that may be very effective in restoring systemic and cerebral perfusion in the acute phase following injury. In

addition to reducing intracranial pressure, these solutions would appear to be superior to mannitol for resuscitation.^{9,10} Whilst it appears that hypertonic saline is a better neuro-resuscitative solution, firm recommendations cannot be made until a number of randomised controlled trials are completed.

The role of routine osmotherapy remains questionable in neurological emergencies and mannitol in particular should be used with circumspection.

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