Pre-emptive analgesia with NSAID—what does it achieve?

Sir,—We wish to comment on the study of Espinet and colleagues [1] who investigated the combined effect of thoracic extradural local anaesthetic block and administration of diclofenac either 30 min before or 30 min after skin incision on post-hysterectomy pain and analgesic consumption. They found that the timing of analgesia made no difference to pain scores or postoperative analgesic requirements, that is there was no pre-emptive effect of diclofenac and extradural local anaesthesia. They discussed these findings in relation to the known actions of non-steroidal anti-inflammatory drugs (NSAID) in inhibiting peripheral sensitization of the primary afferent nerve terminal and so reducing afferent barrage from the periphery. This afferent barrage contributes to central sensitization in the spinal cord and the degree of central sensitization is said to relate to subsequent pain experience and analgesia [2]. The authors comment that the lack of pre-emptive analgesia in their study is at variance with that seen in animal studies using similar paradigms.

While their study was designed carefully to exclude the confounding effects of systemic opioids, nitrous oxide and local anaesthetic test doses, the lack of pre-emptive analgesic effect reported in this study may be explained by central actions of NSAID. In addition, not all types of injury are sensitive to pre-emptive treatment, and under certain circumstances central local anaesthetic block may not prevent the subsequent development of hyperalgesia. These possibilities are discussed below.

It is now well established that prostaglandins contribute not only to peripheral but also to central sensitization, and that NSAID act at central and peripheral sites [3]. In experimental models of central sensitization, intrathecal administration of NSAID results in antinociception [4, 5], and critically, their central action is equally effective whether administered before or after the noxious stimulus. This is because they act on intracellular messengers responsible for the maintenance of the persistent nociceptive state in the spinal cord [6]. In humans, systemically administered diclofenac crosses the blood–brain barrier and CSF concentrations may continue to increase for 12 h after a single dose [7]. Therefore, in the study of Espinet and colleagues [1], a central spinal action of diclofenac, reducing central sensitization with equal efficacy either before or after incision, could potentially have obscured any pre-emptive action of extradural bupivacaine. A recent study using pre-emptive vs post-injury ketorolac did show a small initial opioid sparing effect. However, ketorolac may cross the blood–brain barrier to only a minimal extent and so inhibition of the central nervous system contribution to persistent nociception and hyperalgesia associated with the primary event such as injury discharge would not have been obscured by the central actions of the NSAID in this study [8].

Animal studies also show that pre-emptive analgesia may not be effective in all types of injury. Dougherty, Garrison and Carlton [9] have recently reported [13] that while intrathecal local anaesthetic initially produces profound block of sensory transmission, as the local anaesthetic wears off, a paradoxical state of spinal hyperexcitability results. This may completely mask any previous benefit. More importantly, no subsequent long-term behavioural benefit could be shown from pre-emptive intrathecal lignocaine, even compared with animals which received no intrathecal lignocaine (although in contrast, topical local anaesthetic to the sciatic nerve has previously been shown to be beneficial with this same nerve injury model [14]). The authors also pointed out that the marked clinical benefit shown by Bach, Noreng and Tjellen in their well known study [15] in amputees was achieved using a combination of extradural local anaesthetic and opioid.

Pre-emptive analgesia as a concept has essentially been accepted to relate to inhibition of the afferent barrage, especially the initial “injury discharge” associated with the primary event such as nerve injury. As has been emphasized previously [16], the injury discharge may outlast the treatment and so obscure the benefit implied by some animal studies. Furthermore the following factors: (i) giving drugs that act not only on injury discharge but also on the substrate of the central sensitized state, such as NSAID; (ii) the differential sensitivity, of different types of nerve injury to pre-emptive analgesia; and (iii) the recent experimental evidence that intrathecal local anaesthetic alone may have little benefit in terms of reducing subsequent central sensitization; all help to explain some of the disappointing findings in clinical studies of pre-emptive analgesia but conversely these same observations will help in the design of better regimens to prevent pain.

M.J. HUDSPITH
R. MUNGLANI
University Department of Anaesthesia
Addenbrooke’s Hospital
Cambridge

Cytokine balance and immunosuppressive changes at cardiac surgery

Sir,—The study of McBride and colleagues contains much useful information on the immunological changes associated with surgery [1], but omitted several important aspects. We would welcome the authors’ comments on the following points.

The authors mention briefly that beta adrenoceptor blocking drugs may alter the pro-inflammatory cytokine response, but the possible effect of other cardiac drugs is not considered. Could calcium channel antagonists also have changed the cytokine response? It has been shown in an animal model that administration of calcium antagonists, either before or after endotoxin administration, exerted a protective effect and decreased mortality [2, 3]. Some cytokines exert their effects by increasing free intracellular calcium, especially IL-4, which is one of the principal cytokines in TH2 lymphocyte development [4]. A decrease in intracellular calcium concentration after calcium channel blocker use may decrease amplification of the initial cytokine signal by cytokines in TH2 lymphocyte development [4]. A decrease in intracellular calcium, especially IL-4, which is one of the principal cytokines in TH2 lymphocyte development [4]. A decrease in intracellular calcium concentration after calcium channel blocker use may decrease amplification of the initial cytokine signal by cytokines in TH2 lymphocyte development [4].

In describing the activation of TH2 cells and the increase in IL-10 as key events in an anti-inflammatory response to cardiac surgery, the authors failed to mention that the principal immunological fault after major surgery and trauma is impaired production of TH1 lymphocytes, which are largely responsible for cell-mediated immunity [6, 7]. Development of TH2 lymphocytes is dependent on the early production of IL-4 (TH2 cytokine) in conjunction with down-regulation of interferon gamma and IL-2 [6, 8]. Whether TH2 lymphocyte activity is favoured when TH1 lymphocyte production is suppressed is unclear, but no increase in IL-2 or IL-4 was found during or after cardiopulmonary bypass [9].

The statement that pentoxifylline induces TH2 activity is misleading [10]. This phosphodiesterase inhibitor increases intracellular cAMP concentration which stimulates PGE2 synthesis, resulting in impaired IL-2 synthesis and abnormal TH1 development. Because IL-4 synthesis is not affected, TH2 activity is unaffected. Therefore, preferential TH2 development occurs as a result of inhibition of TH1 lymphocytes [10]. Indeed, failure of IL-2 production is considered to be a major factor in the impaired cell-mediated responses after surgery and trauma [11, 12].

It is clear that there are many factors involved in the immunosuppression after cardiac surgery and the changes in IL-10, IL-1ra and sTNF alpha observed by the authors only play a part.

P. SHEERAN
G. M. HALL
Department of Anaesthesia
St George’s Hospital Medical School
London


beginning with IL-10, 10 min after aortic cross-clamp release and followed by IL-1ra and the TNF soluble receptors over the next 24 h. In the absence of calcium antagonists these children were able to mount a phased anti-inflammatory response [1]. The existence of a phased anti-inflammatory cytokine response cannot therefore be attributed to the presence of calcium antagonists.

It is not yet known what factors if any influence the magnitude of the phased anti-inflammatory cytokine response and what clinical significance variations in magnitude of this phased anti-inflammatory cytokine response may have. Our group is actively investigating this, and it is indeed possible that calcium antagonists (including volatile anaesthetic agents) may influence the magnitude of this response.

The cytokine response in patients and the isolated CPB system differed in that there was no increase in anti-inflammatory cytokines in vitro [2]. Because of the known effects of Ca++ on immune function, Sheeran and Hall advise “great caution” in comparison of the cytokine response within patients and the isolated CPB circuits. Cautious comparison of the two systems indicates that the major difference between patients and the isolated CPB circuits is not the absence of calcium antagonists but rather the fact that within the isolated CPB circuit blood does not have an opportunity to escape from the activating non-endothelialized surface of the CPB apparatus and enter the vasculature of the patient. We believe that this is vital to any interpretation of these differences.

Sheeran and Hall described impaired production of TH1 cytokines as “the principal immunological fault” at major surgery and claimed that we failed to mention in our discussion such an “immunological fault”. There is nothing new in describing the immune response as “being at fault”. For many authors have concentrated on the pro-inflammatory response and immunosuppression at cardiac surgery as two aspects of disordered immunological homeostasis. Sheeran and Hall have simply gone further than most in speculating on the “principal” of these so called “immunological faults”.

We recommend a fresh approach to investigating immunological change at cardiac surgery. We believe that an alternative and helpful way to investigate the immune changes at elective cardiac surgery is to view the immune changes therein as a model of a successful and indeed appropriate response. Most patients for elective coronary artery bypass grafting (CABG) surgery now go home 5 or 6 days later. Surely this is an example of outstanding immunological success! Let clinical outcome be the arbiter as to which aspects of the immune response at cardiac surgery are at fault.

The cardiac surgical patient with good clinical outcome presents an excellent model for study of a successful immune response. We have been the first to highlight the phased anti-inflammatory response as a possible contributor to this success. Other workers have described an IL-10 response after cardiac surgery [3]. We have never suggested that the phased anti-inflammatory response which we have described is limited to IL-10, IL-1ra and TNF soluble receptors. In fact it is likely that IL-4, TGF-β and indeed other as yet undiscovered anti-inflammatory cytokines may play an important role in the success of our patients.

Only when the ingredients of a successful immune response such as occurs at cardiac surgery are understood shall we understand when the immune response is “at fault”. We believe that it is important to know when the immune response is at fault. This information will only come through comparing the profiles of the immune response of cardiac patients who do well with those who (rarely) go on to develop the systemic inflammatory response syndrome (SIRS) or indeed infective complications such as mediastinitis. This knowledge may then enable us to devise effective strategies in the prevention and early treatment of SIRS in the context of major trauma and non-cardiac surgery. We may even be able to predict those patients at risk of developing severe infective complications.

Sheeran and Hall pointed out that our statement that oxpentifyline induces TH2 activity is misleading. We thank them for this and highlight that the preferential TH2 development after oxpentifyline treatment is an indirect result of inhibition of TH1 development by the drug.

Immunomodulation in the treatment of SIRS in the ICU has been largely unsuccessful. An air of despondency has descended upon the literature [4]. This may be because we have been too quick to modulate the immune response without fully understanding what is an appropriate response to trauma and sepsis.

Perhaps it is time to re-evaluate the cardiac surgical patient as a model of success and then re-design our immunomodulatory strategies accordingly.


**Perioperative changes in α-acid glycoprotein concentrations**

Sir,—Booker, Taylor and Saba [1] suggested that preoperative measurement of α-acid glycoprotein (AAG) concentration should be performed in all infants undergoing major elective surgery who are expected to receive prolonged bupivacaine infusions in the postoperative period. This is based on concern that bupivacaine toxicity may be related to low plasma concentrations of the drug binding protein. Unfortunately, this concern is, in turn, based on several dubious premises: (1) that plasma protein binding of drugs may have significant pharmacodynamic implications; (2) that changes in protein binding are important clinically for drugs which are highly bound, such as bupivacaine; and (3) that if variations occur in plasma concentrations of AAG, then free plasma concentrations of the drug can vary considerably, whereas the total concentration of the drug in plasma is only slightly affected. To explain these misconceptions is a long story—I refer the authors to a few recent publications [2, 3].

Premise (3) is the incorrect way round; if the fraction of bupivacaine bound in plasma changes as a result of a change in AAG concentration, classical pharmacokinetic theory predicts that, in the case of a low hepatic extraction drug such as bupivacaine, total plasma drug concentration varies but the unbound drug concentration does not. As it is the latter which determines pharmacological effect at steady state, there would be no clinical consequence of a change in AAG concentration. Therefore, on this basis, measurement of this protein would be a waste of time and resources. One caveat applies to this conclusion, if AAG concentration decreases in proportion to the degree of hepatic dysfunction, then its measurement may be an indirect predictor of the ability of the liver to clear free bupivacaine by metabolism. However, such an association would be independent of the degree of plasma drug binding.

G. T. TUCKER
Department of Medicine and Pharmacology
University of Sheffield
Royal Hallamshire Hospital, Sheffield


British Journal of Anaesthesia
Duke University Medical Center
Durham, NC, USA
M. A. ARMSTRONG
Department of Microbiology and Immunology
Queen’s University of Belfast
Belfast
T. J. MCMURRAY
Royal Victoria Hospital
Belfast
CBF in adults using near infrared spectroscopy (NIRS): potential for bedside measurement?

Sir,—We read with interest the article by Owen-Reece and colleagues [1] and suggest that the findings of NIRS cerebral tissue measurements warrant further discussion. Comparison between scalp and dural recordings in patients allowed conclusions to be made regarding the percentage of the illuminated tissue volume which was cerebral. Measurement of cerebral blood flow (CBF) with the optodes on the dura compared well with values obtained by invasive techniques, but CBF was underestimated by a factor of 3 with the optodes positioned on the scalp. This can be explained by the cerebral tissues contributing only 30–40 % to the total pathlength. Scalp and skull have been shown to have low blood flow and act as static “deadspace” [2]. The chromophore concentration changes detected by NIRS are mostly cerebral, but they must be seen and expressed as concentration changes occurring in the total illuminated tissue volume, 60–70 % of which is extracerebral in the adult. In a rat model [3] and in neonates [4] it has been postulated that the extracerebral component is less than 20 % of the total optical pathlength and this has been accepted as a minor limitation in these measurements. Previous studies by Elwell and co-workers in adults have alluded to the problem of the relatively small component that the cerebral tissue contributes to the total optical pathlength, but none of the less they achieved results for cerebral blood flow comparable with invasive techniques despite using scalp recording [2]. The small cerebral component of the total interrogated volume has major implications for the clinical use of such a system as a small alteration in the cerebral tissue volume has a large effect on the proportions of cerebral and extracerebral tissue in the total illuminated tissue volume and thereby has a major effect on measurements of changes in chromophore concentration. The proportion of cerebral tissue may vary between subjects or even within a subject because of changes in optode/scalp coupling or pathological changes, for example in cerebral oedema when the proportion of brain in the illuminated tissue volume may increase as the brain is forced against the skull. In these circumstances, is the instrument measuring quantified changes in chromophore concentrations occurring in the brain?

It is not specified that figure 1 is a dural recording, but using the values shown to make an estimate of cerebral blood volume this is likely to be the case. If this is a dural recording, the same resaturation event performed with the optodes placed on the scalp would cause a corresponding change in [HbO2] over the initial 4 s of only 0.6 μmol litre−1. This value would be of a similar magnitude to the baseline variability of the trace. The cerebral sulci have little effect on the proportion of cerebral tissue illuminated and also that when the optodes are pressed firmly against the scalp, skin blood flow has negligible influence [Delpy D. T., personal communication]. As stated in our article, it is necessary to determine the contribution of extracerebral tissue to the total optical pathlength before further progress is made. Similar modelling work, which we hope will assist in quantifying the effects of extracerebral tissue on near infrared spectroscopic measurements, is also in progress at UCL Department of Medical Physics and Bioengineering. The authors are correct in interpreting figure 1 as a dural recording and we apologize that this was not made clear. As they imply, the signal-to-noise ratio is a significant problem in measurements made via the scalp and more scalp measurements were rejected than those from dura. Desaturation–resaturation is unlikely to be harmful for the reasons outlined in the article. However, we agree that it may be preferable to avoid the technique in brain-injured patients. There is a range of cerebral haemodynamic variables which can be observed using NIRS which do not affect arterial oxygen saturation, for example cerebral blood flow measurement using indocyanine green as a tracer, spontaneous cerebral blood volume changes, cerebral vascular response to altered PaO2, and mean cerebral saturation.

In view of the progress being made in dealing with the scaling problems of scalp recording and the scope for other cerebral measurements which can be made non-invasively with NIRS, we agree with Hopton, Walsh and Lee that the potential of the technique is exciting. There is a great deal of work still to be done before it is suitable for widespread clinical use.

H. OWEN-REECE
C. EVELWELL
W. HARRNESS
J. GOLDSTONE
D. DELPY
J. WYATT
M. SMITH
Departments of Anaesthesia, Medical Physics and Bioengineering UCL Hospitals London
Departments of Anaesthesia and Surgery National Hospital for Neurology and Neurosurgery Queen Square, London

Hypercoagulability induced by crystalloids

Sir,—The *in vitro* study by Ruttmann, James and Viljoen [1] in which dilution of blood with saline and Haemaccel was shown to render it hypercoagulable, is fascinating reading. Their results not only challenge intuitive assumptions but also have possible implications for our clinical practice and, perhaps more importantly, call into question the methodology of studies designed to assess the effect of regional anaesthesia on the development of postoperative thromboembolic disease (TED).

The authors cite the *in vivo* study of Janvrin, Davies and Greenhalgh [2] in which patients given crystalloid in the perioperative period (*"wet"* group) had a higher incidence of deep vein thrombosis (DVT) than those who received none (*"dry"* group). While this is of course no criticism of Ruttmann, James and Viljoen, it is worth pointing out that this frequently cited study involved only 60 patients and its power was in the region of 0.65 [3].

However, the results of the *in vitro* work of Ruttmann, James and Viljoen are compelling, and notwithstanding the above criticism, if the *in vitro* effect is real then this may present a case for the use of the hydroxyethyl starches (HES) where there is a risk of TED, and where plasma volume expansion is required. This colloid, rather than promoting coagulation, prevents it by inducing a mild and transient type-I von Willebrand-like syndrome [4].

Over the years, several studies have demonstrated to varying degrees the effect of extradural and spinal anaesthesia on the reduction in postoperative thromboembolic disease compared with general anaesthesia. The proposed mechanisms whereby this is effected include reduced blood loss and transfusion requirements, reduced stress response and its concomitant procoagulant effect, improved lower extremity blood flow, and reduction in plasminogen activator inhibitor-1 (PAI-1) in those receiving regional anaesthesia [5–7]. In none of these studies was administration of crystalloid and colloid considered to exert any specific effect on coagulation. Only administration of blood was standardized between the groups. In most reports, the design of the study ensured that haemodynamic variables were controlled tightly and this usually implied that those receiving extradural or spinal anaesthesia were preloaded with up to 15 ml kg\(^{-1}\) of lactated Ringer’s solution and required ongoing plasma volume expansion with this and similar solutions throughout the case and into the postoperative period to achieve “target” haemodynamic values (although the actual volumes were not recorded).

Again, if the procoagulant effect of crystalloid haemodilution is real then it may to some extent mask the beneficial effects of regional anaesthesia if crystalloid is used to preload these patients, and this may provide support for the argument that normotension should be maintained either with vasopressors or HES. Clearly, this work needs to be re-evaluated in the light of any new understanding of the effect of crystalloid haemodilution.

A. D. FARMERY
A. KONG
Department of Anaesthetics
Ipswich Hospital
Ipswich


Sir,—We agree fully with the comments that our results challenge intuitive assumptions and we agree entirely with the inferences they draw from these results. Furthermore, as Farmery and Kong correctly point out, our results may indeed call into question not only the methodology of studies designed to assess the effect of regional anaesthesia on the development of postoperative thromboembolic disease, but also the methodology of most of the currently quoted studies designed to assess the effect of any of the colloids on coagulation, as the majority use a crystalloid control group.

Whether or not our *in vitro* results can be translated to the clinical situation remains to be resolved. However, we are currently in the process of investigating this effect in human volunteers and the results appear to be consistent with our *in vitro* work. Indeed, using standard tests of coagulation and also thrombelastography, we have been able to further strengthen our hypothesis that haemodilution renders blood hypercoagulable.

We can only agree with the comments of Farmery and Kong that the role of crystalloid solutions needs to be re-evaluated, especially in those circumstances in which the prevention of procoagulant states is desirable.

T. G. RUTTMANN
M. F. M. JAMES
J. F. VILJOEN
Department of Anaesthesia
University of Cape Town
South Africa