Endogenous heparin-like substances and their effect on thromboelastography and postoperative graft function after orthotopic liver transplantation

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Liver transplantation is associated with severe coagulopathy, especially after graft reperfusion. Thromboelastography (TEG) is routinely used to monitor clotting and guide product transfusion. Previous small studies have reported a heparin-like effect seen on post-reperfusion TEG.1 2 This effect may be due in part to release of glycosaminoglycans by the vascular endothelium. Endothelial cells are known to produce heparan sulphate and also bind other heparin-like substances, for example, dermatan and chondroitin sulphate.3 This heparin effect may also be caused by exogenous administration of heparin to the donor liver before transplantation.

The aims of this project were to audit blood product use (whether they were being transfused in accordance with our TEG-based guideline) and to investigate whether a heparinoid effect was apparent in our patients. We further sought to determine its relationship with postoperative graft function.

We performed TEG without clot activator after induction of anaesthesia, before and after graft reperfusion as part of clinical routine in 364 patients. Samples were analysed in ‘native’ and ‘heparinase-treated’ cuvettes. Data are expressed as mean (SD).

Our use of fresh-frozen plasma (FFP) significantly correlated with TEG variables r, k, and x (P<0.0001, r²=0.37). However, platelet and cryoprecipitate transfusion did not appear to be guided by TEG. A positive heparinoid effect was seen in 90% of patients. The coagulation time [r+k] was 52.0 (28.0) min (native) vs 35.2 (17.7) min (heparinase-treated). The mean ratio was 1.84 (1.22). In a multiple linear regression model, postoperative liver function (alanine aminotransferase activity) was significantly correlated with ‘heparinoid effect’ (assessed by native/heparinase-treated [r+k] ratio), with age, gender, and diagnostic category, P=0.04. However, the heparinoid effect did not correlate with hard outcome measures.

We have shown that although the use of FFP appeared to be rational, transfusion of platelets and cryoprecipitate did not appear to be guided by TEG. A clinically relevant heparin effect exists after liver reperfusion in orthotopic liver transplantation in 90% of patients. This effect is related to postoperative liver function. The explanation for this observation requires further investigation but does not appear to presage worse overall outcome.

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Adiponectin expression in skeletal muscle and its response to lipopolysaccharide treatment

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Adipose tissue is an endocrine organ which produces signalling proteins involved in inflammation and glucose homeostasis.1 One of these proteins, adiponectin, promotes glucose utilization and fatty acid oxidation. Adiponectin has previously been thought to be an adipose-specific molecule; however, recent evidence suggests expression in skeletal and cardiac muscle and endometrial tissues.2–5 In this study, we investigated skeletal muscle adiponectin expression levels and the effect of lipopolysaccharide (LPS) treatment in mice and C2C12 mouse myocytes.

LPS (Escherichia coli O 111:B4) 25 mg kg⁻¹ was injected intraperitoneally (i.p.) under general anaesthesia (nitrous oxide 2% isoflurane) into 8–10-week-old male C57BL/6J mice (Charles River, UK). Control animals received equivalent volumes of normal saline (n = 6/group, 24 total). Mice were...
killed at 4 or 24 h by cervical dissociation. Soleus muscle depots were removed and immediately frozen in liquid nitrogen. mRNA levels were determined by PCR. RT–PCR was performed in a 12.5 μl reaction volume consisting of 12.5 ng of reverse-transcribed cDNA mixed with optimal concentrations of primers and probe and qPCR™ Core kit (Eurogentec, UK) using an Mx3005P detector. Sequencing of PCR product was performed using the Nucleospin PCR clean-up gel extraction. Statistical significance was determined using the Mann–Whitney U-tests. The threshold for significance was \( P < 0.05 \).

RT–PCR indicated that the adiponectin gene is expressed in skeletal muscle (adipose tissue was used as a positive control), and sequencing of the PCR product confirmed a 100% match for adiponectin mRNA. C2C12 myocytes (\( n = 6 \), all groups) were then used to verify the presence of adiponectin mRNA in skeletal muscle cells. Adiponectin mRNA level was reduced in skeletal muscle in mice after i.p. injection of LPS by 6.9-fold (\( P < 0.05 \)) and 30-fold (\( P < 0.001 \)) in the 4 and 24 h cohorts, respectively. In C2C12 myocytes, there was a significant reduction in adiponectin gene expression after high doses of LPS (5 and 10 μg ml⁻¹), resulting in a 2.94- and 2.17-fold (\( P < 0.05 \)) reduction in mRNA, respectively.

Our results build on the increasing evidence that modulation occurs in the adiponectin system during inflammation. Previous authors have demonstrated a reduction in adipose tissue expression of adiponectin after LPS treatment. We have demonstrated that adiponectin mRNA is present in mouse skeletal muscle which is in agreement with other authors. Confirmation of adiponectin mRNA in isolated myocytes assists in ruling out contamination by peri-muscular fat. In vivo, there was a rapid marked reduction in adiponectin after treatment with high-dose LPS. This change is also seen in isolated myocytes. Adiponectin was until recently believed to be an adipose-specific molecule; however, in the light of studies showing its presence in other tissues, this has been disputed. It is therefore interesting, not only to confirm the presence of its mRNA in skeletal muscle but also to show a significant down-regulation in vitro and in vivo in response to LPS stimulation. Skeletal muscle is an insulin-sensitive tissue and hyperglycaemia and insulin resistance are common in sepsis, and therefore, this may imply a role for the adiponectin system in sepsis in tissues other than adipose tissue.

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Functional electrical impedance tomography by evoked response: monitoring for asymmetry in awake and anaesthetized patients

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Functional electrical impedance tomography by evoked response (fEITER) is a novel imaging device which monitors changes in cerebral conductivity at 100 frames per second across the whole brain. We aimed to evaluate cerebral asymmetry using fEITER in relation to the depth of anaesthesia, as measured with bispectral index (BIS).

Six ASA I or II patients undergoing elective surgery gave written, informed consent. Thirty-two Zipprep™ (Covidien, UK) electrodes were placed on the patient’s scalp using the...
levels (BIS and left hemispherical fEITER measurements at higher BIS anaesthesia with bilateral BIS. fEITER measures sub-second observed a significant difference (n group, anaesthesia with either 20 ml of levobupivacaine 0.5% (TAP block under ultrasound guidance after induction of anaesthesia delivering morphine 0.5 mg every 10 min i.v. on demand. The primary objective was to study morphine consumption in such patients receiving TAP block is comparable with control subjects over 24 h after operation.

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Effect of magnesium on analgesia from intrathecal local anaesthetics and fentanyl: a meta-analysis
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Intrathecal magnesium has been shown in rats to potentiate opioid antinociception, with minimal adverse effects. Prospective randomized controlled trials (RCTs) have examined the effect of magnesium given with local anaesthetics, opioids, or both, to assess its role as an adjunct to spinal anaesthesia. This meta-analysis examines the findings from these RCTs.

The keywords human, intrathecal, magnesium, and obstetric were entered into Medline and EMBASE with no language restrictions to identify RCTs and published abstracts from scientific meetings. The Jadad scale2 was used to assess the quality of the manuscripts, which all scored between 3 and 5. RevMan statistical software6 utilized inverse variance and a random effect model to calculate standardized mean difference with 95% confidence intervals for continuous variables. The primary outcome was duration of analgesia.

Postoperative pain after renal transplantation may be severe, but administration of systemic opioids is limited by impaired renal function and the risk of respiratory depression. Transversus abdominis plane (TAP) blocks have been shown to be effective after a variety of abdominal procedures,5 as they provide opioid-sparing effects and improve patient satisfaction.5 There has been no randomized controlled trial to evaluate the efficacy of TAP blocks in renal transplant recipients.

Forty-eight recipients were randomized to receive TAP block under ultrasound guidance after induction of anaesthesia with either 20 ml of levobupivacaine 0.5% (TAP group, n=24) or 20 ml of 0.9% normal saline (control group, n=24). After operation, all patients received paracetamol 1 g i.v. or orally every 6 h and patient-controlled analgesia delivering morphine 0.5 mg every 10 min i.v. on demand. The primary objective was to study morphine consumption in the first 24 h after surgery. Secondary outcomes included assessment of the degree of sedation, respiratory depression, nausea and vomiting, and pruritus. Pain scores (visual analogue scale 0–10) were measured by nursing staff blinded to the randomization, in theatre recovery, and at 3, 6, 12, and 24 h after operation in the ward. All variables were compared between the two groups using the Wilcoxon signed-rank test.

Two patients were excluded from the TAP group due to protocol violation. Fentanyl and morphine consumption were similar intraoperatively in both groups. There was no difference in pain scores between the two groups in the recovery room, but morphine consumption [mean (sd)] at this time in the TAP group was less than the control group [2.2 (3.75) vs 4.1 (2.8) mg, P=0.009]. There was no significant difference in total morphine consumption over 24 h [12.8 (7.4) vs 14.3 (14.3) mg, P=0.7] between the groups. No difference was recorded in pain scores, sedation scores, respiratory depression, nausea and vomiting, or pruritus between the two groups at any time point. Post hoc analysis demonstrated a significant negative correlation between the age of the patient and the amount of self-administered morphine at 12 and 24 h (P=0.006).

TAP blocks in renal transplant recipients only offer better pain relief in the immediate postoperative period. Morphine consumption in such patients receiving TAP block is comparable with control subjects over 24 h after operation.

References

Unilateral transversus abdominis plane block for renal transplant recipients
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Postoperative pain after renal transplantation may be severe, but administration of systemic opioids is limited by impaired renal function with the risk of respiratory depression.1–3 Transversus abdominis plane (TAP) blocks have been shown to be effective after a variety of abdominal procedures,1–3 as they provide opioid-sparing effects and improve patient satisfaction.5 There has been no randomized controlled trial to evaluate the efficacy of TAP blocks in renal transplant recipients.

(time from intrathecal injection to the first analgesic request). Secondary outcomes were: onset of sensory block, time to maximal sensory block, onset of motor block, time to complete motor recovery, and total morphine consumption after operation.

Thirteen studies of 841 patients published between 2002 and 2010 were included. Addition of intrathecal magnesium increased duration of spinal analgesia (286 min in the magnesium group vs 195 min in controls, \( P < 0.00001 \)). Magnesium did not exert a significant effect on the onset of sensory or motor block, but led to a reduction in morphine consumption after operation (Table 1).

The addition of intrathecal magnesium may increase duration of spinal analgesia and reduce morphine consumption after operation, without any delay in time to maximal sensory block. With minimal side-effects, magnesium has a role as an adjunct in spinal anaesthesia.

### References

### Radial artery to digit pulse transit time is highly pressure-dependent

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Pulse transit time (PTT) can give a non-invasive measure of arterial pressure.\(^1\) It is often measured from the ECG R-wave to the trough of the photoplethysmograph wave. A typical PTT to the finger of a young subject is about 200 ms. Pressure wave transmission in the arterial system is related to several factors\(^2\) which may affect the use of this index. We considered factors in the arterial system of the hand, by compressing the ulnar and radial arteries at the wrist.

We recorded ECG, non-invasive radial artery pressure (Colin CBM-700), finger photoplethysmograph, and finger pulses in 12 volunteers. Signals were digitized at 10 kHz (Micro1401plus, CED). We detected waveform troughs and peaks using second derivatives and defined ‘RaDt’ as the time from minimum radial artery pressure to the minimum of the photoplethysmograph waveform. Data were analysed with Octave and Prism5 (GraphPad). We modified arterial pressure in the hand by pressure on the radial or ulnar artery. All fingers gave similar results. Data are from the middle finger and are median (quartiles).

The pressure and photoplethysmograph timing were affected similarly by arterial compression. Figure 2 shows typical recordings from the middle finger in subjects with radial and ulnar artery dominance.

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Transcutaneous electrical acupoint stimulation for pain relief and decreasing opioid-related side-effects after total hip arthroplasty in elderly patients

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Transcutaneous electric acupoint stimulation (TEAS) has been considered as an effective alternative therapy for various types of pain. However, randomized controlled studies have not yet been done for treatment of acute pain after total hip arthroplasty (THA) in elderly patients. In this study, we investigated whether TEAS has any effect on complementary analgesia after THA compared with a sham control treatment.

Sixty-eight elderly patients were enrolled (Beijing, China) and randomly divided into two groups. Six cutaneous self-adhesive electrode pads, sized 16 cm2, were attached on the four acupoints (bilateral P6, LI4; ST36, GB312 ipsilateral to the surgery site) and connected with a HANS Acupoint Nerve Stimulator. Group A received true TEAS in which all patients were stimulated in the standard dense-and-disperse (D–D) mode at a frequency setting of 2/100 Hz for 30 min before incision and at 2, 4, 20, and 44 h after operation. The patients in Group B received an identical intervention as in Group A but without electric stimulation. The intensity of stimulation was set at 0 mA for Group B and at 9–20 mA for Group A (depending on the patient’s ability to tolerate the stimulation). Patient-controlled analgesia (PCA) was used in both groups for 2 days after operation. The amount of postoperative fentanyl via PCA and pain intensity on a visual analogue scale (VAS-10) were used to assess analgesia. The incidence of analgesia-related side-effects to fentanyl and optional medication use were recorded.

Sixty patients completed the procedure (30 TEAS vs 30 sham controls). There was no difference in pain intensity on VAS-10 between two groups at 24 and 48 h after operation during rest or ambulation. However, Group A required 37% and 31% less fentanyl than Group B at 24 and 48 h after surgery, respectively. The incidence of analgesic-induced side-effects such as nausea, vomiting, and dizziness was significantly higher in Group B than Group A. The frequency of rescue medication in Group A was significantly lower than Group B.

Transcutaneous electric acupoint stimulation is an effective and complementary approach to reduce postoperative analgesic requirement and related side-effects in elderly patients after THA.

Imaging neural responses to affective and pain-related stimuli in chronic non-malignant pain patients vs healthy controls

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The meaning of pain, in terms of its perceived physical and psycho-social causes and consequences, is different in chronic non-malignant pain (CNMP) compared with acute pain. This can affect the threat value of pain and the way in which it demands attention.1,2 There is a need to develop methods to investigate naturally occurring changes in chronic pain and responses to pain cues. The majority of functional magnetic resonance imaging (fMRI) studies to date have focused on experimental acute pain and then made inferences about CNMP. This study investigated neural activity in affective and attentional regions in chronic pain patients vs healthy controls, as assessed by fMRI using a non-painful stimulus.

Fifteen CNMP (≥3 months) patients with predominantly musculoskeletal pain were recruited and age and gender matched to healthy controls. All participants initially had a practice run in the mock scanner before scanning was performed on a 3T MR Scanner (GE Healthcare). During one acquisition (T2*-weighted for blood-oxygen level-dependent contrast), subjects were shown activity of daily living photographs taken from the Photograph Series of Daily Activities database, a validated tool for assessing kinesiophobia. These photographs had already been validated in a previous study by the authors. Patients were asked to think about how they would feel, mentally and physically, if asked to undertake this activity and rate their anxiety using a button box. Additionally, a T1-weighted structural scan was acquired for data processing. Participants were also asked to complete a number of questionnaires on pain, function, fatigue, and mood.

Various well-established pain regions showed significant activation in the patients compared with the healthy control subjects. The CNMP patients also showed significant activation in the default mode network (DMN) during the task; the DMN is typically characterized as regions of the cortex which are inactive during a task and active at rest in healthy subjects. The behavioural questionnaires illustrated that CNMP significantly affected the quality of patients’ lives.

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These findings demonstrate that chronic pain has a widespread impact on overall brain function, and aberrant DMN activity may underlie the cognitive and behavioural impairments accompanying chronic pain, supporting Beliki and colleagues’ proposition. This aberrant activity is thought to lead to the frontal lobe cortical loss and abnormal brain ageing seen in patients with CNMP. Using this method, we have assessed the impact of CNMP without inflicting acute, experimental pain, and established a method that could be used in future research to examine whether these brain changes can be reversed.

Acknowledgement
Welsh Institute of Cognitive Neurosciences Grant.

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Heterologous desensitization of human GPR55 receptors
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There is growing evidence for a role for cannabis/cannabinoids in pain medicine, but there is debate as to the members of the cannabinoid receptor (CB) family. Current and well-accepted CB-receptors are classified as CB1 and CB2. However, there are two other orphan GPCRs; GPR55 and GPR119 which may be members of this family. GPR55 is coupled to increases in [Ca2+]i, via the G-protein G13. In this study, we examined the desensitization profile of human GPR55 expressed in human embryonic kidney (HEK; HEKGPR55) cells using [Ca2+]i as a readout.

HEKGPR55 (provided by AZ or untransfected negative control) cells were loaded with Fura2 (5 μM; a Ca2+ indicator dye) and intracellular Ca2+ ([Ca2+]i) was measured as we have described previously. Cells were pre-stimulated with the muscarinic agonist carbachol (CCh: varying concentrations) for 120 s, then a fixed concentration of the GPR55 agonist L-α-lysophosphatidyl inositol (LPI, 1 μM) was added. Next the reverse experiment was performed, pre-stimulation with LPI followed by a fixed concentration of carbachol (1 mM). Concentration–response curves were analysed to obtain potency (pEC50) and efficacy (Emax) using GraphPad Prism V5 and data are presented as mean±SEM.

In HEKGPR55, LPI produced a concentration-dependent increase in [Ca2+]i, with a pEC50 of 6.71 (0.08) and an Emax of 75 (9) nM (n=9). In untransfected HEK cells, there was an increase in [Ca2+]i, at 3 and 10 μM. Therefore, 1 μM was chosen as the concentration that selectively activated GPR55. CCh produced a concentration-dependent and saturable increase in [Ca2+]i, with a pEC50 of 4.98 (0.16) and an Emax of 123 (18) nM (n=5). CCh produced a concentration-dependent and saturable inhibition of the 1 μM LPI response with a pEC50 of 4.99 (0.24) and an Emax of 47 (4)% (n=5). LPI produced a concentration-dependent and saturable inhibition of the 1 mM CCh response with a pEC50 of 7.60 (0.15) and an Emax of 30 (4)% (n=5). There was a difference between the desensitization and primary LPI responses (P<0.05, unpaired t-test).

We confirm that LPI is capable of activating GPR55, but care is required at high concentrations. GPR55 undergoes heterologous bidirectional desensitization when expressed in HEK cells, but the degree is small. There was a ~10-fold difference in the potency for LPI to activate and desensitize, but this was not observed for CCh and may result from differences in lipophilicity.

References

Clinical comparison of Macintosh vs Glidescope blade tip proximity to neck skin surface during laryngoscopy
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In a previous study explaining the ‘Peardrop Effect’ as a mechanism for difficult Macintosh laryngoscopy, reference was made to disposition of the blade tip when the tongue’s ‘inevitable residual volume’ has to be accommodated in the submandibular space. A necessary corollary of this hypothesis is that all other things being equal, increased distance from the neck skin surface to the blade tip should lead to worse laryngoscopic view. To study this problem, we planned a clinical trial in 24 patients to compare Macintosh laryngoscopy with the Glidescope video laryngoscope.

Crico-thyroid membrane and sternal notch landmarks were marked before operation (as proxies for the laryngeal inlet). Each patient had consecutive laryngoscopies with Macintosh and then Glidescope. At maximum glottic exposure (recorded as POGO score, ‘Percentage of Glottic Opening’), lateral neck photographs were taken using a fixed distance from the patient’s midline. Equivalent photographs of each device on its own were also taken. Images were imported into ‘CorelDRAW Graphics Suite’ (v. X3) and
Bezier outlines of the blades were produced. These were then overlayed onto the lateral photographs to determine the blade tip positions relative to the neck surface.

Figure 3 plots differences (Glidescope minus Macintosh) in the POGO score and blade tip to skin proximity (in cm). Glidescope POGO scores were better than Macintosh in 13 of 24 patients (the same in seven; worse in four). Skin proximity was the same for both (i.e. $-0.1$ to $+0.1$ mm) in four, with Glidescope closer in 16 and further away in four.

Overall, despite our expectations, there was no clear gradation in POGO results relative to the blade tip–skin distance for either Macintosh or Glidescope. However, this overlay method is likely to prove useful in comparing indirect laryngoscope blade tip positioning (i.e. functionality)\(^2\) relative to Macintosh.

References

Efficacy of pre-emptive bilateral superficial cervical plexus block in thyroid surgery: a meta-analysis

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Bilateral superficial cervical plexus block (BSCPBJ) is used in patients undergoing thyroid surgery for postoperative pain relief. There have been several randomized controlled trials (RCTs) comparing it performed before skin incision with that done at the end of surgery, with or without saline control. We conducted this meta-analysis to assess the influence of pre-emptive BSCPBJ on postoperative analgesia requirements.

The keywords bilateral cervical plexus block and thyroid surgery were entered into Medline and EMBASE with no language restrictions to identify RCTs and published abstracts from scientific meetings. We found eight RCTs of 766 patients published between 2001 and 2010 in which ropivacaine with or without clonidine or bupivacaine/levobupivacaine with or without epinephrine had been used. The Jadad score\(^1\) was 2–5 for the RCTs retrieved. The primary outcome variable was the number of patients requiring postoperative rescue analgesia in the pre-incision group. Secondary outcomes were: the number of patients requiring rescue analgesia who had BSCPBJ performed at the end of surgery, intraoperative analgesic requirement in both groups, and length of hospital stay in the pre-incision group. Dichotomous data were summarized using the odds ratio (OR), M–H method, and continuous variables by inverse variance and standardized mean difference. Analyses were done using Review Manager V5.1 software and the random effects model.

If given pre-emptively, BSCPBJ probably reduces postoperative analgesic requirements and length of hospital stay, but has no significant effect on intraoperative

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of patients/ RCTs</th>
<th>OR (95% CI)(^*)</th>
<th>SMD (95% CI)(^*)</th>
<th>P-value</th>
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<td>1.14 (−1.4, 3.67)(^*)</td>
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<td>Length of hospital stay (pre-incision only)</td>
<td>241/2</td>
<td>0.35 (0.08, 0.61)(^*)</td>
<td></td>
<td>0.01</td>
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</tbody>
</table>

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If given pre-emptively, BSCPBJ probably reduces postoperative analgesic requirements and length of hospital stay, but has no significant effect on intraoperative
analgesia usage (Table 2). Further good randomized controlled trials are required.

Reference

Isoflurane induced prostate cancer chemotherapy resistance in vitro
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Surgery is the most effective treatment for solid tumours. Recently published work showed that anaesthetic techniques, anaesthetics, or both may have an impact on cancer recurrence after surgery, although the responsible mechanisms for those remain elusive. Chemotherapy is often used before, during, or after surgery. Furthermore, any potential interactions between anaesthetics and chemotherapy on cancer progression remain unknown. The aim of the present study is to investigate whether isoflurane can induce resistance to chemotherapy in prostate cancer in vitro and the potential mechanisms behind this.

Human prostate cancer cell (PC3) line (a gift from Dr Charlotte Bevan from Hammersmith Hospital, London, UK) was cultured and then treated with 2% isoflurane in air balanced with 5% carbon dioxide for 2 h, while cells in the control group were exposed to air balanced with 5% carbon dioxide only. After gas exposure, the cells were recovered with normal culture media for 24 h. Cells were then cultured in a medium containing docetaxel at doses up to 100 nM for another 48 h and subjected to cell viability assessment with MTT assay. Other cohort cultures were exposed to isoflurane up to 2% under normoxic conditions at 37°C for 2 h. Cell lysates were harvested at 0 h time point up to 24 h after isoflurane exposure for western blotting to measure HIF-1α expression.

HIF-1α expression was also determined with in situ immunofluorescent staining.

IIn vitro

Isoflurane exposure increased cell viability in the presence of docetaxel at the doses tested from 10–75 nM. The overall viability was significantly increased by 13% as assessed by area under the curve. Isoflurane exposure also increased HIF-1α expression in a time-dependent manner with a maximal increase by more than 200% (P<0.05) 24 h after isoflurane exposure. Isoflurane treatment enhanced HIF-1α expression in a concentration-dependent manner with a maximal increase of about 200% (P<0.05) at the highest studied concentration of 2% isoflurane. Immunofluorescent staining revealed that HIF-1α was remarkably upregulated in the cytoplasm and readily translocated into nuclei while these phenomena were not found in cells in the absence of isoflurane exposure.

Isoflurane induces resistance to chemotherapy in prostate cancer cells, which may be mediated by HIF-1α up-regulation.

Reference

Is a reduced albumin concentration effective for albumin dialysis?
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Despite major advances in acute liver failure, prognosis remains poor with a 33% mortality rate and 25% transplant rate in the USA. In 2010, the number awaiting a transplant has increased by 11%, with an average waiting time of 149 days. Two patients die every week while awaiting a transplant. Modern methods available to support patients with acute liver failure, either as a bridge to transplantation or to substitute some of the lost liver functions, can be broadly classified into artificial and bio-artificial (cell-based) techniques. The molecular adsorption and recirculation system is an FDA-approved albumin dialysis liver support system. Single-pass albumin dialysis (SPAD) provides some advantages, including significantly less albumin usage and non-proprietary equipment. However, the minimum effective albumin concentration in the dialysate solution has not been established.

Following on from our initial studies in a model simulating patients with acute liver failure, we set out to determine the lowest dialysate albumin concentration necessary to achieve adequate bilirubin clearance. Serial experiments (Table 3) were conducted using human albumin in concentrations of 4%, 2%, 1%, and 0.5% against a patient compartment spiked with 10 mg dl⁻¹ bilirubin in 4% human albumin solution. A standard hollow fibre dialyser membrane was incorporated in the circuit and flow rate adjusted to 200 ml min⁻¹ on the patient side vs 10 ml min⁻¹ on the dialysate side.
Our serial experiments and photometric assay confirmed consistent reduction of bilirubin concentration on the patient side accompanied by simultaneous increase in bilirubin concentration in the waste bag across all dialysate albumin concentrations. Significant bilirubin clearance was achieved at 1% albumin dialysate concentration.

Our results suggest that lower albumin concentration can be used effectively to facilitate bilirubin clearance. This is in keeping with previous studies. Less human albumin utilization will have a significant cost implication and improve the clinical feasibility of SPAD.

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Effects of melatonin in a rat model of sepsis
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The mortality rate of patients with sepsis-induced organ failure remains high. The precise pathogenesis of such organ failure is unknown, but oxidative stress-mediated mitochondrial damage occurs. In our in vitro studies, we have shown that melatonin and its metabolite 6-hydroxymelatonin reduce oxidative stress and mitochondrial dysfunction.1

We assessed the effect of melatonin on plasma creatinine concentration (renal function), alanine aminotransferase activity (ALT, hepatic cellular function), and interleukin-6 (IL-6) levels after a septic insult in a rat model. Rats (~500 g) were anaesthetized with isoflurane and a tracheostomy was performed to permit ventilation. To allow i.v. access, a cannula was inserted into the tail vein. Rats were then randomly allocated to receive either saline alone, a 1 ml bolus of i.v. 0.1 mg kg⁻¹ lipopolysaccharide plus 1 mg kg⁻¹ peptidoglycan G (LPS/PepG), followed by either a bolus of melatonin (3 mg kg⁻¹ i.v.) or saline. All animals then received an i.v. infusion of saline. After 6 h, blood and tissue was removed for analysis.

Creatinine, ALT, and IL-6 were higher in animals which received LPS/PepG compared with saline only (Fig. 4). In rats treated with LPS/PepG plus melatonin, creatinine, ALT, and IL-6 were lower than LPS/PepG and saline.

We have shown that melatonin treatment results in decreased biochemical measures of organ dysfunction after an inflammatory insult. We have also shown that melatonin reduces IL-6 concentrations in a rat model of sepsis.

Reference
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Patient safety incidents associated with displaced or obstructed tracheostomies: comparison of levels of harm between critical care and ward environments
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Patients with tracheostomies have a greater chance of some harm occurring if an airway incident occurs on a hospital ward compared with incidents occurring in intensive care units (ICU)1 2 (OR = 7).3 The aim of this study is to compare the severity of harm occurring in these locations when a tracheostomy incident occurs.

Fig 4 Creatinine, ALT, and IL-6 in rats treated with saline only, LPS/PepG plus saline, or LPS/PepG plus melatonin.

Creatinine (µmol litre⁻¹)

150
200
250

ALT (units ml⁻¹)

0
500
1000
1500
2000

IL-6 (ng ml⁻¹)

0
100
200
300
400
500
600
700

Saline only
LPS/PepG plus saline
LPS/PepG plus melatonin
We identified patient safety incidents associated with airway devices reported to the UK National Patient Safety Agency over a 2 yr period.\(^2\)\(^4\) Post-placement tracheostomy incidents were stratified into three ordered strata: completely or partially displaced and obstructed. Outcomes were scored in ascending ordered categories of severity from 1 to 6.\(^5\) The effects of location, incident, and outcome were analysed using log-linear analysis of multi-way contingency tables. Linear mixed model analysis using maximum likelihood estimation of the log-transformed scores was performed with the Kruskal–Wallis and Mann–Whitney U used as backup tests. The Cuzick test was used for trend in ranks. Results are presented as geometric mean with 95% confidence interval (CI). Significance was defined at \(P<0.05\) (two-sided) with Bonferroni corrections as appropriate.

A total of \(n=494\) incidents were classified by location into ICU (\(n=218\)) or ward (\(n=276\)). Harm scores were significantly higher for ward incidents vs ICU (log-linear \(P=0.011\)). There was a significant trend, with increasing severity scores, from complete through partial displacement, to tube obstruction (Cuzick’s \(P<0.0001\)). The interaction of location and incident demonstrated significant differences in harm scores occurring with a completely displaced tracheostomy on the ward \([2.14 (95\%\ CI 2.03–2.25)]\) vs ICU \([1.55 (1.42–1.69),\) Mann–Whitney’s \(U P<0.0001]\).

While ward patients would be expected to be less dependent than ICU patients, they come to greater harm when a tracheostomy incident occurs. Different levels of staffing, observation, equipment, and infrastructure may account for the difference in severity arising from the completely displaced tracheostomy incidents. Respiratory distress with a partially displaced or obstructed tracheostomy may alert staff, whereas complete displacement may result in a delayed diagnosis if not immediately observed.\(^5\) In ICUs, complete displacement may be more likely to result in a trial without the device if the patient is in a weaning phase, whereas ward patients usually require a long-term tracheostomy, necessitating replacement. Airway intervention (such as replacing the tracheostomy) is classified as ‘harm’ in the reporting system, which may partly explain the observed differences.

### Table 4 Median [range (IQR)] LOS (days) (Mann–Whitney’s \(U\)). Mortality, readmission rate, and transfusion requirements are presented as number of patients (%) (Fisher’s exact test)

<table>
<thead>
<tr>
<th></th>
<th>Anaemic ((n=51))</th>
<th>Non-anaemic ((n=49))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (LOS)</td>
<td>17 [4–48 (11–31)]</td>
<td>7 [3–40 (5–11)]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1 yr mortality</td>
<td>20 (40%)</td>
<td>6 (12%)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>30 day readmission rate</td>
<td>14 (27%)</td>
<td>4 (8%)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Required blood transfusion</td>
<td>42 (82%)</td>
<td>7 (14%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Is preoperative anaemia associated with a poorer outcome after colorectal cancer surgery?


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The potential adverse outcomes associated with perioperative blood transfusion are widely documented.\(^1\)-\(^4\) Less is written about the impact of preoperative anaemia, and more specifically, its use as an independent predictor of outcome and the benefit of non-transfusion correction before cancer surgery. Here we look specifically at the consequence of preoperative anaemia in colorectal cancer surgery patients at a large tertiary centre in the UK.

Electronic records of all 100 patients undergoing colorectal cancer resection surgery from August 2009–February 2010 were reviewed and each patient identified as anaemic or non-anaemic according to local reference ranges (11.1 g dl\(^{-1}\) female, 13.1 g dl\(^{-1}\) male) and the lowest preoperative haemoglobin seen. Length of stay and red blood cell transfusion requirements were pre-specified primary endpoints. Secondary outcomes were readmission rate and mortality. Genders were combined for data analysis.

The preoperative haemoglobin [mean (range)] was 10.0 g dl\(^{-1}\) (5.9–12.8) for anaemic patients (\(n=51\)), and 13.9 g dl\(^{-1}\) (11.3–16.6) for the non-anaemic patients (\(n=49\)). The groups were similar in terms of age, gender, ASA grade, and American Joint Committee on Cancer grading. Preoperative anaemia was associated with a statistically significant difference in terms of length of stay, transfusion requirements, readmission rate, and mortality at 1 yr.

As illustrated in Table 4, we have found that preoperative anaemia is associated with inferior outcomes after colorectal cancer resection surgery. A formal trial is required to determine the nature of this association, and whether correction of preoperative anaemia is beneficial.

### References

Viscosity of echogenic and non-echogenic needles in the Thiel cadaver

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Despite the introduction of ultrasound technology, no reduction in the incidence of postoperative neurological damage has been observed. A recent innovation in needle design, the echogenic regional block needle, has an intermittent textured surface which increases the reflection of ultrasound waves. Echogenic single-shot needles show improved viscosity at steep needle insertion angles (in-plane) and shallow needle insertion angles (out-of-plane) compared with non-echogenic needles.

An echogenic Tuohy needle (Pajunk, Newcastle, UK) has since been introduced and an opportunity existed to assess the visibility of this new needle.

Therefore, the primary objective of this study was to compare the visibility of the echogenic Tuohy needle (ET) [SonoLong], with an echogenic single-injection needle (ES) [SonoPlex] and a non-echogenic Tuohy needle (NT) [PlexoLong]. Secondary objectives were to compare tip visibility and needle visibility scores in-plane and out-of-plane at different angles (30°, 45°, 60°, 75°). For power analysis, in-plane mean visibility scores were assumed to be 3, 3, and 2 for the ET, ES, and NT, needles, respectively, and 3, 3, 1.5, and 1.5 for the 30°, 45°, 60°, and 75° needle angles.

Using a randomized block, ANOVA power analysis with three needles and four angles, 72 injections were needed within six blocks, and a total of 144 to account for in-plane and out-of-plane injection.

For the study, an independent operator managed the randomization, study conduct, and data collection, and another performed ultrasound scanning and needle injection. Two anaesthetists acted as independent assessors of visibility using a five-point Likert score, with 0, poor visibility, and 5, excellent visibility. Needles were inserted 3 cm in and out of the biceps and deltoid muscles of a Thiel-embalmed cadaver. Needle movement was seen using ultrasound (Zonare, Palo Alto, CA, USA) and video recorded. Statistical analysis used NCSS, Utah, and Vassarstats.com.

Visibility data were non-parametric. Correlation between raters was 0.72 [95% confidence interval (CI): 0.63–0.81] using weighted k. Agreement was 0.67 (95% CI: 0.56–0.76). In-plane, median [inter-quartile range (IQR)] visibility scores were 4.5 (3.5–5.0), 4.5 (3.75–5.0), and 2.5 (2.0–3.0) for the ET, ES, and NT needles, respectively, P<0.001 using the Friedman test. The needle tip was visible in 79%, 83%, and 25% of insertions. Out-of-plane, the median (IQR) visibility scores were 3.75 (3–4.25), 3 (2.75–4), and 2 (1.5–2.5), P<0.001, for the ET, ES, and NT needles, respectively.

In conclusion, the ET and ES needles are more visible than the standard NT needle both in-plane and out-of-plane.

Reference


Substrate oxidation during exercise: switch with age?

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Preoperative carbohydrate (CHO) loading is a key component of the enhanced recovery programme. However, there is little published work on how ageing individuals respond to a CHO load during stress. The aim was to investigate age-related changes in substrate oxidation when an i.v. glucose load is delivered during exercise.

After Ethical Committee approval, 12 trained healthy male volunteers were recruited: eight young and four older. In addition, data from four older subjects from a previous experiment were considered separately. Each subject underwent two experiments: the first involved a standardized exercise protocol (40 min of steady-state cycling at 60% peak oxygen consumption) under the conditions of a hyperglycaemic glucose clamp (infusion of 20% w/v D-glucose to maintain the serum glucose at 10 mmol litre−1). The second or control experiment followed the same exercise protocol, but 0.9% w/v saline was infused instead of glucose. CHO and fat oxidation rates were estimated from respiratory measurements taken at 20 and 40 min of exercise. Data are presented as mean (sd) or 95% confidence interval (CI) and analysed using repeated-measures ANOVA with Tukey’s post-tests and linear mixed models. Two-sided P<0.05 was defined as significant.

Ages were 22.4 (2.9) and 69.0 (7.6) yr in the younger (n=8) and older (n=4) groups, respectively. There was a significant effect of age group on CHO oxidation during exercise (P=0.0025), with the younger group demonstrating higher CHO oxidation rates (2.19 g min−1; 95% CI 1.84–2.54) compared with the older group (0.98 g min−1; 95% CI 0.48–
1.48). Glucose infusion significantly (*P*=0.04) enhanced CHO oxidation in the younger group by 0.29 g min⁻¹ (95% CI 0.016–0.56). In the older group, glucose infusion resulted in a non-significant reduction of CHO oxidation of −0.38 g min⁻¹ (95% CI −3.36 to 2.57). Although the difference in fat oxidation of 0.22 g min⁻¹ (95% CI −0.073 to 0.52) due to age group was not significant (*P*=0.13), there was a significant interaction (*P*=0.0088) of age group and infusion, with fat oxidation increased in older and decreased in younger subjects during glucose loading. Sensitivity analysis including the four older subjects from a previous experiment supported the findings.

During exercise, it appears that glucose loading enhances oxidation of CHO in younger and fat oxidation in older subjects. This implies that there may be a possible switching of substrate preference which is age-dependent.

**Acknowledgement**

This study was funded by Liverpool John Moores University.

**Reference**


**Use of the peri-anaesthetic care unit as a critical care facility: evidence for adverse outcomes**

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At times of peak pressure, post-anaesthetic care units (PACUs) are increasingly used as a critical care overspill facility. We therefore aimed to establish the current use of a tertiary regional unit PACU as an overflow critical care facility and to compare patient outcomes between patients admitted via PACU and directly to ITU. We hypothesized that patients admitted via PACU suffered worse outcomes in terms of increased ITU mortality, length of stay and period of ventilation.

Patients admitted between December 1, 2010, and March 31, 2011, were considered. Patients were identified using the Ward-Watcher ITU management system. Admissions via PACU were also discovered through informal recording methods instituted by PACU staff. Where data were available, age, sex, and ICNARC and APACHE II scores were compared between PACU and direct admissions. Overall length of ITU stay and total ventilated days were compared. Results were analysed using the SPSS statistics package.

No single method of recording of ITU admissions via PACU was found. Recording was spread between the Ward Watcher system, and informal records instituted by PACU staff: paper sheets and a hand-written book. During the period, 279 ITU admissions were identified. Seventy-six patients were admitted via PACU. Data were not present for 32 patients. Forty-four patients had recorded ICNARC and APACHE data. The PACU and direct-admission groups did not show significant differences in age, sex, or ICNARC or APACHE II scores, with mean APACHE II predicted mortalities of 35.9% (PACU) and 36.3% (Direct). ITU mortality was not significantly different (PACU 26.6% vs Direct 27.27%, *P*>0.05). PACU-admitted patients on average had a total length of stay of 11.6 days (SD 14.7, median 4.4 days; inter-quartile range (IQR) 1.8–16.2 days) vs 4.5 days (SD 7.8, median 2.1; IQR 1.0–4.4) for direct admissions (*P*=0.0002, Mann-Whitney *U*-test). PACU-admitted patients had a mean number of ventilated days of 9.9 days (SD 14.6, median 3.8; IQR 1.2–12.0) vs 2.1 days (SD 2.9, median 1; IQR 0.0–3.0) for direct admitted patients (*P*<0.0001, Mann-Whitney *U*-test). The Trust tariff of £1760 per ITU bed day was used to calculate financial implications. The 32 patients lost to Ward Watcher data represent £253 440–£653 312 in lost directorate revenue. The 76 patients considered represent an extra 539.6 bed days, at a cost of £949 696.

Our findings support the hypothesis that a lead-time in PACU is detrimental to subsequent patient care in terms of resource utilization. Our data are not sufficiently robust to comment on ultimate outcome as it is difficult to ensure like-for-like admissions because of the haphazard nature of clinical and managerial data recording. We recommend a single, rigorous method of recording ITU admissions via PACU should be instituted. All admissions via PACU should be coded in compliance with the ICNARC minimum data set. Until more robust data are available, all such admissions should be flagged as critical incidents and a management response be sought. Length of stay and ventilated days should be considered in any decision regarding PACU admission vs inter-hospital transfer. A need for PACU admission should be regarded with grave concern as a deteriorating Critical Care bed crisis.

**Fig 5** Antinociceptive effect of UFP-505 and morphine, in the TF assay. a, *P*<0.05, increased compared with saline. b, *P*<0.05, decreased compared with UFP-505 (10 nmol).
Antinociceptive effects of the bifunctional opioid UFP-505

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Morphine used in chronic cancer pain activates MOP(μ) opioid receptors producing analgesia and tolerance.¹ If DOP(δ) receptors are concurrently blocked, analgesia with reduced tolerance results.¹ UFP-505 is an MOP agonist/DOP antagonist² and here we present first in vivo use in rats.

We have studied i.t. (catheter L5/L6 interspace) drug administration in male Wistar rats. Antinociception was assessed using the tail-flick (TF) assay by recording TF latency (TFL) in response to radiant heat (cut-off 15 s) before treatment (baseline), then at 15, 30, 60, 90, and 120 min. Drugs were administered either acutely or after repeated administration (in 20 μl volumes). Acutely, multiple doses of UFP-505 (1–50 nmol i.t.) and morphine 10 nmol were administered and their TFLs were assessed in order to determine the equianalgesic doses. In repeated dosing (up to 5 days), 10 nmol UFP-505 or 10 nmol morphine was administered i.t. once daily and TWL assessed. Spinal cord and frontal cortex quantitative-PCR for MOP and DOP receptor gene transcription³ are presented for acute (120 min) administration. Data are mean (SEM) (n).

Catheter retention was a major problem. Acute antinociceptive data for UFP-505 and morphine are shown in Figure 5 (day 1 repeated administration data were similar). After 3 days repeated administration, there was a reduced response to morphine, but not UFP-505. In spinal cord MOP and DOP, mRNA increased after acute morphine and UFP-505 (~2-fold, P<0.05). In frontal cortex MOP and KOP, mRNA increased after acute morphine and UFP-505 (2–4-fold, P<0.05). These data indicate that MOP/DOP bifunctionals may provide antinociception with reduced tolerance.

Acknowledgement

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References