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ABSTRACTS

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Formation of inflammatory plateletleucocyte aggregates in vitro and their adhesion to inflamed endothelial cells

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In sepsis, there is extensive formation of inflammatory platelet leucocyte aggregates (PLAs) that circulate and adhere to inflamed vascular endothelium. PLAs correlate with severity of disease. Whole blood stimulation assays and flow cytometry are widely used to study blood PLAs formed in vitro in response to pathogen associated molecular patterns (PAMPs, most commonly LPS). However, this approach lacks robust methodology. For example, the extent of spontaneous formation of PLAs ex vivo is often unclear. Thus, a reliable in vitro model to investigate sepsis relevant formation of PLAs



Fig 1. Transmission electron micrograph of platelet and leucocyte engaging with endothelial cell as indicated.

and their adhesion to inflamed endothelial cells is required. We aimed to develop a model of the acute inflammatory reaction to common bacterial PAMPs, on which to test therapeutic agents.

Whole blood from healthy volunteers was drawn and immediately immunolabelled with anti CD66b-APC and anti CD42b-PE to assess the extent of spontaneous PLA. Further, whole blood samples were incubated with either endotoxin (E. coli 0111: B4 or Salmonella enteritidis, Sigma), as single PAMP, or heat killed bacteria (Klebsiella pneumoniae or Staphylococcus aureus, departmental archive), for 1h at 37°C. PLAs were identified by flow cytometry as CD66b and CD42b positive events. Ultrastructural analysis of these aggregates was performed by scanning electron microscopy (Scanning EM). Whole blood was stimulated with LPS (1000 ng/ml), heat-killed K. pneumoniae or heat killed S. aureus (106 CFU/ ml) or left unstimulated (control), then co-incubated with TNFa stimulated EAhy.926, to investigate PLA adherence to inflamed endothelial cells by transmission electron microscopy (TEM) and light microscopy. Secreted IL-8 was measured by ELISA. Data were analysed using the Kruskal-Wallis test, followed by Dunn's test for multiple comparisons between groups.

Twelve individual samples were tested from eight volunteers. There was significant spontaneous aggregation of platelets and leucocytes, which was not enhanced by LPS from E. coli or S. enteritidis. Scanning EM revealed similar PLA surface area between unstimulated and endotoxinstimulated samples but a significant increase after whole blood stimulation with heat killed bacteria (p<0.0001). Light microscopy and TEM (Fig. 1) showed adherence of more complexed cellular aggregates on the endothelial layer after stimulation with heat killed bacteria, in conjunction with a significant increase in IL-8.

Unexpectedly, LPS was not a suitable stimulus to develop an in vitro model of acute cellular interactions between PLAs and inflamed endothelium. Rather, the combination of heat killed bacteria and Scanning EM successfully modelled formation of complex PLAs and their adhesion to endothelial cells.

Nociceptin/Orphanin FQ (NOP) receptor is differentially expressed on glial cells

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Glial cells constitute the majority of the cellular components of the CNS. They are involved in a wide range of physiological and pathological conditions including immunomodulation, neuropathic pain, and opioid tolerance¹. Opioid receptors are classified into classical (MOP, DOP and KOP) and non-classical (NOP). NOP receptor has been found to play a central role in pain processing and opioid tolerance². In this study, we screened for the expression and function of the NOP receptor on glial cell lines.

The pattern of NOP receptor expression at the level mRNA (qPCR)³ and protein ([leucyl-³H] N/OFQ saturation binding)⁴ was studied in a range of glial cell lines including 1321N1 human astrocytes, C6 rat astrocytes, MO3.13 human oligodendrocytes, HOG human oligodendrocytes, and EOC-20 mouse microglia. NOP receptor activity was assessed using a scratch wound healing/cell migration assay at a fixed time of 30 hours⁵.

1231N1, MO3.13, and HOG but not EOC-20 cells expressed NOP mRNA⁶. In addition, C6 cell lines were found to express NOP receptor mRNA. Furthermore, 1231N1, MO3.13 and HOG expressed NOP protein in a radioligand binding assay. Highest expression of mRNA was in MO3.13 and in radioligand binding was in HOG and 1321N1⁶. In lines that expressed NOP receptor protein, we assessed the activity of N/OFQ, a structurally inactive derivative (desPhe1-N/OFQ) and the metabolically stable derivative PWT-N/OFQ. In both astrocytes (1321N1) and oligodendrocytes (MO3.13 and HOG) N/OFQ and PWT-N/OFQ but not desPhe1-N/OFQ (all at 1 μ M) reduced wound healing (migration), Table 1. NOP receptor is differentially expressed in a range of glial cell lines where it was functionally active. Interestingly there is no expression on microglia. Further studies in primary glial cell cultures are underway.

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Development and characterisation of a novel fluorescent NOP ligand-N/OFQATTO

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The opioid receptor family is comprised of four members, the naloxone-sensitive Mu (μ), Delta (δ) and Kappa (κ) receptors, as well as the naloxone-insensitive NOP receptor. Activation of the NOP receptor has been shown to influence, amongst others, pain pathways, anxiety and depression. In the periphery, NOP activity has been implicated in immune cell function, heart failure and sepsis.¹ While it is possible to measure NOP receptor protein levels in certain tissue, the sparsity of available protein in peripheral cells often means NOP expression is implied through functional studies. In this current study, we demonstrate the capability of a red fluorescent peptide based on the endogenous ligand for NOP (Nociceptin/Orphanin FQ; N/OFQ), N/OFQATTO to identify NOP receptors in various expression systems.

Confocal microscopy and radioligand binding ([³H]-N/OFQ) was used to characterise binding of N/OFQATTO in Human embryonic kidney (HEK) cells expressing the NOP receptor or green fluorescent tagged (GFP) NOP receptors.² For assessment of N/OFQATTO binding in low expression systems, human polymorphonuclear cells were extracted from whole blood using density gradient centrifugation and binding of N/OFQATTO measured using confocal microscopy. All data are mean±SEM of at least 5 experiments.

In [³H]-N/OFQ binding assays N/OFQATTO bound with high affinity (pKi: 8.98±0.09) and selectivity for the NOP receptor, behaving in a similar manner to unconjugated N/OFQ (9.03±0.05). Using confocal microscopy, it is possible to measure increases in fluorescence (binding) in a concentrationdependent manner, allowing the affinity of N/OFQATTO to be determined (pKd: 8.53±0.34). N/OFQATTO binds to the surface of polymorphonuclear cells, an event that can be blocked by the high affinity NOP antagonist SB 612,111 or unlabelled N/ OFQ, indicating selective binding to NOP receptors on the cell surface. In high expression systems, tracking of N/OFQATTO allows for determination of NOP receptor internalisation postactivation. Furthermore, coupling of N/OFQATTO to NOP receptors tagged with green fluorescent protein allows for visualisation of both ligand and receptor interaction.

Table 1 The effect of NOP ligands on wound healing /cell migration of glial cells, data (% wound healing) from n=5, * = $P\leq0.05$ after 30 hrs compared to control (ANOVA)

Cell type	Control	N/OFQ	PWT-N/OFQ	desPhe1-N/OFQ
1321N1 astrocytes	55.6±2.0	$42.5\pm5.8^{*}$	$35.8 \pm 1.8^{*}$	50.0±1.8
MO3.13 oligodendrocytes	31.1±2.7	$22.0\pm0.7^{*}$	21.0 ± 1.9^{*}	29.0±2.9
HOG oligodendrocytes	33.5±3.2	$26.1\pm2.5^{*}$	24.8 ± 3.4^{*}	30.6±3.7

Conjugation of the N/OFQ peptide with the red fluorescent ATTO dye has not altered the functional properties of this peptide. The detectable range of N/OFQATTO in confocal microscopy is such that concentration-dependent binding; binding affinities can be measured.

The sensitivity of N/OFQATTO in low expression system experiments is such that binding of this ligand can be seen on polymorphonuclear cells, demonstrating the presence of NOP receptor protein on these cells for the first time. N/OFQATTO is a versatile and robust ligand that will act to further understand localisation and function of the NOP receptor.

Acknowledgments

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Effects of isoflurane on dopaminergic neurone synaptic vesicle exocytosis

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Despite widespread clinical use of anaesthetics, their pharmacological mechanisms of action are poorly understood. Volatile anaesthetics such as isoflurane induce a reversible state of amnesia, unconsciousness, and immobility in response to painful stimuli.¹ At the cellular level, volatile anaesthetics exert prominent effects on synaptic transmission. While these synaptic effects involve predominately postsynaptic actions, data from our laboratory support presynaptic mechanisms as well.² At presynaptic sites, anaesthetics differentially inhibit synaptic vesicle (SV) exocytosis depending on neurone phenotype, with greater inhibition of excitatory glutamatergic SV release than of inhibitory GABAergic SV release from hippocampal neurones.^{3,4} However, anaesthetic effects on dopamine release from dopaminergic (DA) neurones have not been studied, even though dopaminergic mechanisms have been implicated in emergence from anaesthesia.5

We investigated the effects of isoflurane on SV release in DA neurones (identified by post hoc tyrosine hydroxylase immunoreactivity) from rat ventral tegmental area (VTA) neurones using live-cell imaging to measure SV exocytosis and Ca^{2+} influx. We employed a pH-sensitive variant of eGFP (pHluorin) fused to the luminal domain of the vesicular monoamine transporter (vMAT) to measure exocytosis and the cell permeant fluorescent Ca^{2+} indicator Fluo-5F to measure intracellular Ca^{2+} concentration.

Isoflurane differentially inhibited SV exocytosis and Ca^{2+} influx induced by electrically stimulated action potentials from both DA (by $29 \pm 4\%$, n = 13, p < 0.0001 and $42 \pm 3\%$, n = 6, p < 0.0001, respectively) and non-DA neurones (by $16 \pm 5\%$, n = 10, p < 0.0055 and 58 ± 5%, n = 8, p < 0.0001, respectively). In contrast to other neurotransmitter phenotypes, isoflurane also inhibited SV exocytosis evoked by elevated K⁺ in DA neurones, suggesting a voltage-gated Na⁺ channel (Nav) independent mechanism of anaesthetic action in this neuronal population. This contrasts with SV exocytosis from glutamate or GABA releasing neurones, which requires Nav. SV release is known to be tightly coupled to Ca²⁺ entry⁶. The degree of inhibition of SV exocytosis by isoflurane in DA neurons was proportional to the reduction in Ca^{2+} influx, and could be mimicked by reducing extracellular Ca²⁺ concentration. Use of subtype-specific voltage-gated Ca²⁺ channel toxins revealed that SV exocytosis in DA neurones was solely mediated by P/Qtype and N-type Ca²⁺ channels. Isoflurane inhibited SV exocytosis mediated by both P/Q-type and N-type Ca²⁺ channels by a Nav-independent mechanism, supporting a role for inhibition of these Ca²⁺ channel subtypes in the presynaptic effects of isoflurane in DA neurones.

These findings shed light on the presynaptic targets of isoflurane in DA neurones, and provide a molecular target for isoflurane induced unconsciousness and emergence from isoflurane anaesthesia.

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Nociceptin/Orphanin FQ (N/OFQ) is neuroprotective in an ex vivo mouse model of cerebral ischaemia

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Cerebral ischemia is a leading cause of death and disability in the UK with limited treatment options.¹ The Nociceptin/ Orphanin FQ (N/OFQ) receptor, NOP, and its endogenous ligand N/OFQ, are non-classical members of the opioid receptor family.² Central activation of NOP results in general inhibition of neurotransmitter release, in particular glutamate,² which contributes to cell death following cerebral ischemia. Activation of NOP by N/OFQ or other small molecule agonists would therefore be predicted to be neuroprotective. Here, we have assessed NOP expression in hippocampal and subcortical regions of the mouse brain by PCR and assessed the effects of activation in an *ex vivo* model of cerebral ischaemia.

We used C57/BL6j neonatal mice, aged 6-9 days. For NOP expression studies, mRNA was extracted from hippocampal and subcortical regions using a tri-reagent methodology, and cDNA formed via reverse transcription. cDNA was probed for NOP relative to the house-keeper gene Beta-actin, using Taq-Man probes via QPCR.³ To investigate the neuroprotective properties of NOP activation, an *ex vivo* model of cerebral ischemia was used where cortical brain slices were exposed to oxygen and glucose deprivation (OGD) to mimic ischemic damage, in the presence/absence of N/OFQ. Brain slices were immersed in artificial cerebral spinal fluid (aCSF) to recover from slicing prior to OGD exposure in the presence/absence of N/OFQ (1 μ M) for 40 minutes. Slices were incubated with 2% 2,3,5-triphenyl-2H-tetrazolium chloride (TTC) to visualise infarcted tissue.⁴ Area of cell death including hippocampus and sub-cortex but excluding the outer cortex was measured using Imagej software 1.51.

NOP receptor mRNA was expressed in both tissues with deltaCt, relative to Beta-actin of 10.52 * 0.25 and 9.62 * 0.65 in hippocampus and sub-cortex respectively (mean + SEM from 9 mice across 3 litters). Subcortical tissue expressed 1.87 fold more NOP than hippocampal tissue. In an acute model of cerebral ischaemia OGD increased the area of cell death from $25.92 \pm 4.09\%$ (in normoxic condition) to $66.02 \pm 9.99\%$ (Data are mean \pm SEM from 12 neonatal mice, across 4 litters; p<0.01). Treatment with N/OFQ significantly (p<0.01) reduced this ischaemic damage to $39.47 \pm 7.82\%$. The vehicle for N/OFQ, dH₂O, was ineffective; 72.09 \pm 11.87% compared to OGD control.

These data show a neuroprotective role for NOP activation and suggest this pathway as a potential target in acute ischaemic stroke. Further studies, with more metabolically stable NOP agonists are underway and a series of *in vivo* experiments planned.

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Consequences of dynamic changes in palmitoylation of Nav1.5 voltage-gated Na⁺ channels

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Inhibition of cardiac Nav1.5 voltage-gated Na⁺ channels (VGSCs) contributes to toxicity by local anaesthetics (LAs). Inhibition is state-dependent; channels become more sensitive to block when inactivated. Nav1.5 undergoes palmitoylation, the addition of palmitoyl groups to intracellular cysteines, affecting Nav1.5 inactivation. Mutations associated with inherited arrhythmias disrupt Nav1.5 palmitoylation causing inactivation at more hyperpolarised potentials¹. This may enhance their block by LAs increasing the vulnerability of affected individuals to toxicity. We are investigating whether palmitoylation influences state-dependent inhibition by the LA, lidocaine. However, it is unclear whether palmitoylation is a dynamic process or occurs through altered Nav1.5 expression. We therefore initially examined the consequences of acute inhibition of palmitoylation by 2-bromopalmitate (2-BP) on Nav1.5 function.

Whole-cell voltage-clamp was used to record from HEK293 cells transiently expressing Nav1.5². Currents were evoked by depolarising from -80 mV and 2-BP was bath-applied. Current-voltage relationships and the voltage-dependence of activation and inactivation were established as described previously ². Data are expressed as mean \pm SEM. Comparisons were made using the paired Student's t-test.

Acute application of 2-BP (1 μ M) caused a reduction of 44 ± 4.5% (n = 12) in the peak Nav1.5 current amplitude elicited by depolarising from -80 to 0 mV, reducing peak current density from 487 ± 46 pA/pF to 205 ± 28 pA/pF (n = 12, p < 0.0001). The voltage-dependence of activation was shifted in the depolarising direction. The half-maximal voltage (V½) of activation changed from -30 ± 0.7 mV to -24 ± 1.7 mV (n = 12, p < 0.01). The slope of the activation curve was also significantly affected in the presence of 2-BP (8.8 ± 0.6 vs 14 ± 0.7, n = 12, p < 0.0001). The voltage-dependence of inactivation was shifted in a hyperpolarising direction, with a significant change in the V½ of inactivation from 75 ± 1.8 mV in control to -90 ± 2.3 mV in the presence of 2-BP (1 μ M) (n = 12, p < 0.0001).

Our results demonstrate that acute inhibition of palmitoylation shifts the voltage-dependence of inactivation in the hyperpolarising direction. A greater likelihood of inactivation caused by the absence of palmitoylation may enhance sensitivity to inhibition of Nav1.5 by LAs. We are currently investigating the effect of the palmitoylation status of Nav1.5 on block by lidocaine.

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Dexmedetomidine alleviates LPS-induced pyroptosis in astrocytes in vitro

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Pyroptosis is a highly inflammatory form of programmed cell death associated with sepsis and major traumatic injury.^{1,2} Neuroinflammation is considered to "cause" brain dysfunction including cognitive decline in various clinical conditions including critically patients in ICU.³ Dexmedetomidine, an a2-adrenergic receptor agonist, is widely used in perioperative medicine as a sedative, which possesses potential anti-

inflammatory properties.⁴ This study aims to examine whether dexmedetomidine could attenuate LPS-induced pyroptosis in astrocyte cultures.

The human astrocytoma cell line (1321N1) was cultured and treated with LPS (1–100 ng/ml) in the absence or presence of dexmedetomidine (0.1 μ M) for 24 hours. The pyroptosis executioner gasdermin D (GSDMD) and NLRP3 inflammasome (ASC-caspase1) expression, histone translocation, and cell death were assessed in various experiments using western blot, immunofluorescent staining and propidium iodide flow cytometry, respectively.

LPS caused cell death in a dose-dependent manner. Pretreatment with dexmedetomidine significantly decreased cell death from 30% induced by 100ng/ml LPS to 14.6% (p < 0.01). Dexmedetomidine also significantly decreased LPS-induced ASC, caspase1 and GSDMD expressions (all p < 0.05). Histone translocation was detected after the cells were treated with LPS whilst histone was still located within the nuclei in the majority of the cells and cellular integrity was also maintained with dexmedetomidine pretreatment.

Our data suggest that dexmedetomidine provides protective effects via attenuating pyroptotic cell death triggered by LPS in astrocytes. Further study is needed to determine the underlying mechanisms and reproducibility in an *in vivo* setting.

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High Definition transcranial Direct Current (HD-tDCS) stimulation over the primary motor and insular cortex reduces capsaicininduced pain and hyperalgesia: a placebocontrolled study

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There is an increasing interest in the use of non-invasive brain stimulation to modulate cortical activity for treating pain and psychiatric disorders. One such method is transcranial Direct Current Stimulation (tDCS) which has a reasonably high safety profile with few side effects and easy to administer. A number of studies reported that it can relieve neuropathic, musculoskeletal and visceral pain as well as headaches and migraine. High Definition Transcranial Direct Current Stimulation (HD- tDCS) is a refinement of the tDCS method and aims to focus the area of stimulation to a specific brain region. We have tested this technique targeting a novel brain area in a human model of experimental pain. In a sham-controlled singleblinded trial we investigated the effects of HD-tDCS over two cortical targets: the primary motor cortex and the insula in a human model of capsaicin-induced pain.

Thirty healthy volunteers (14 female, mean age 32.8 years) were divided into 3 groups and all had capsaicin cream (0.075%) applied for 30 minutes on a 9 cm² area of skin on the volar surface of both arms. The areas of hyperalgesia after capsaicin application were measured by mapping the areas of primary and secondary hyperalgesia using a brush, a 19 g-Von-Frey Filament, and a calibrated 40 g-pinprick (Neurotips). Ten volunteers in each group then received 20 minutes of anodal HD-tDCS (2 mA) targeting the left primary motor cortex, left insular cortex or sham-placebo stimulation. Cortical targeting for stimulation was determined after running computer simulated brain conductivity models. Cutaneous areas of hyperalgesia were re-mapped after stimulation. The visual analogue pain scale was repeated throughout the experiment for assessing pain severity.

We found a significant reduction in subjective pain scores (VAS) and areas of primary and secondary hyperalgesia after motor or insular cortex HD-tCDS compared to sham stimulation. The effects of insula stimulation appear to be bilateral while the reduction in cutaneous hyperalgesia was mainly contralateral to motor cortex HD-tCDS. We found that volunteers in the stimulation groups also reported a significantly faster reduction in pain scores compared to the sham group. The volunteers failed to differentiate whether they had active or sham stimulation.

In a human model of capsaicin-induced pain, anodal HDtCDS of motor and insula cortex was shown to reduce pain and hyperalgesia compared to sham stimulation. This study shows that it is possible to stimulate the insular cortex using HD tCDS and the effects are bilateral as opposed to motor cortex stimulation where reduction in pain and hyperalgesia is predominantly contralateral.

Effect of a single dose of i.v. parecoxib on postoperative pain: a systematic review and meta-analysis

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Parecoxib is the only parenteral selective COX-2 inhibitor available for use within the United Kingdom. It was licensed in 2002 for the treatment of short-term post-operative pain. This metaanalysis aimed to evaluate the impact on postoperative pain of a single dose of parecoxib administered pre- or intraoperatively.

Using PRISMA guidelines all relevant published studies were identified by searching for entries indexed in PUBMED, EMBASE and CENTRAL. The primary outcome was pain at rest in the immediate postoperative period, expressed on a 100 mm visual analogue scale. Secondary outcomes were cumulative consumption of rescue analgesia in the immediate postoperative period and in the 24 h following surgery as well at the incidence of common side effects.

Following abstract screening and full text review, 39 studies published between 2003 and 2015, involving 3,448 patients

were included. Analysis showed a small reduction [-6.47 (-8.78, -4.17), P<0.00001] in postoperative pain intensity reported by patients treated with parecoxib compared to controls. Small reductions in the use of rescue analgesia in both the immediate postoperative period and 24 h following surgery were also seen in patients treated with parecoxib. No studies reported any serious adverse events related to parecoxib administration.

The impact of parecoxib, when used in this manner, appears to be limited to a small improvement in postoperative analgesia that is unlikely to be of clinical significance. As such, there is insufficient evidence to recommend the use of a single dose of parecoxib administered during the hour before surgery or intraoperatively at the doses studied.

Assessment of sleep in patients with chronic pain

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Patients with chronic pain commonly complain about poor sleep and likewise people with poor sleep report worse pain. In NHS Grampian Patients attending chronic pain clinics are routinely assessed using the Brief Pain Inventory (BPI). This is a short questionnaire capturing the severity of patients' pain and the extent to which pain interferes with daily functioning, including one question about interference of pain with sleep. There are several dedicated validated tools available for the subjective assessment of sleep. In this pilot study we asked patients with chronic pain to complete the Pittsburgh Sleep Quality Index (PSQI), the Pain and Sleep 3-Item Questionnaire (PSQ-3) and the Verran-Snyder Halpern (VSH) sleep scale in addition to the BPI, to assess whether the sleep interference score in the BPI was able to accurately capture sleep quality.

Following ethical approval and written informed consent, unselected participants were recruited from pain clinics following provision of information about the study a week before the clinic visit. Fifty-one patients (aged 18–88 years) were recruited. BPI pain scores (patients' assessment of their average pain) were subsequently divided into tertiles of mild (scoring 0–4), moderate (5–6) or severe pain (7–10).

Thirteen participants scored their average pain as mild, 16 as moderate and 22 as severe. BPI sleep interference scores correlated significantly with pain scores (r=0.78, p<0.0001). Sleep disturbance and poor sleep efficiency/quality were identified by the dedicated sleep assessment tools, with significant associations with pain severity tertile. Using the VSH scale which describes sleep over the previous 24h, we found greater sleep disturbance (p=0.014) and poorer sleep efficiency (p=0.012) as pain severity increased (Fig. 2). Likewise using the PSQ-3 which records sleep interference over the last week, sleep disturbance was greater (p<0.0001) and using the PSQI, which assesses sleep over the previous month, the index of poor sleep quality was higher (p<0.0001) as pain increased.

We conclude that more severe pain is associated with worse subjective sleep quality and that the BPI may be useful for rapid initial assessment of sleep in patients with chronic pain.



Fig 2. Non-parametric linear regression of VSH sleep disturbance with BPI average pain score in patients with chronic pain (n=51).

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Current variation in the practice of measuring post-operative pain outcomes: time for a national consensus?

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The 2014 SNAP-1 audit reported that 49.5% of patients experienced moderate or severe postoperative pain¹. There is currently no consensus as to which tools should be used to measure and record post operative pain, with variation in clinical, audit and research practice². To assess whether a national consensus of core outcome measures in post-operative pain is necessary or desired, a survey of current UK practice and opinion was undertaken. A paper-based survey was distributed to all attendees at the National Acute Pain Symposium (NAPS), held in September 2017.

Questionnaires were completed by 114 (63%) delegates, including 57 Acute/Chronic pain nurses, 44 Consultants or Associate Specialists in Anaesthesia and/or Pain Medicine, 9 Specialty Trainees in Anaesthesia, 3 Allied Health Professionals and 1 Orthopaedic Surgeon. 57% delivered services at tertiary referral hospitals. Almost all respondents cared for adult patients, with 36% having a paediatric caseload, and 20% responding to obstetric referrals.

Outcome data were collected routinely by 60% of respondents. Forty-four percent used an excel spreadsheet for analysis, 16% used specialist medical databases, and others reported using paper-based departmental records or the Electronic Patient Record (EPR).

All respondents reported using more than one post-operative pain assessment tool, with 17 different scoring tools currently used across the UK. The most commonly used were the Verbal Rating Scale (75%), Visual Analogue Scale (54%), Numerical Rating Scale (60%), FACES (50%) and the Abbey Pain Scale, for patients who are unable to verbalise (39%).

Most centres recorded pain on both movement and rest (83%), though a number of individuals reported that their new EPR systems would not allow this. Psychological components of pain experience were rarely assessed (10%), mostly in response to referral for complex pain issues rather than as part of routine practice.

Whilst only 31% of respondents were aware of local trust guidelines for post-operative pain assessment, 71% were aware of national guidelines. Four percent of respondents disagreed that a national consensus on post-operative pain outcome measurements would be of value to their clinical practice and for use in local quality improvement initiatives.

The results of this national survey reveal variation in practice in the methods of measuring and recording postoperative pain outcomes and a desire to determine a national consensus of which core outcome measures should be used to guide best practice and allow for a more rigorous approach to improvement science in acute pain. Individual units could use this set of core outcome measures, to submit to a national database to enable benchmarking, and to drive co-ordinated quality improvement.

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Postoperative pain after total knee replacement. Which non-steroidal antiinflammatory drugs should be used?

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Postoperative pain after total knee arthroplasty is a major concern for both patients undergoing the procedure and doctors, as it is difficult to control and can be quite extreme. Currently, a mixture of NSAIDs and opioids is commonly used in order to alleviate the pain, however it is still not known which NSAIDs are the most effective in terms of pain management and side-effect control. Accordingly, there are no respective guidelines. The aim and objective of this structured review was to search, identify, review and critically appraise the existing articles, relevant to the topic.

The study was designed as a systematic review, focusing on the selection/usage of NSAIDs in postoperative pain management in patients after total knee replacement.

The online databases (PubMed¹ and Scopus²) were searched and articles that met the inclusion criteria – i.e. Randomised controlled trials; articles published after 01/12/ 1999; specific procedure – total knee arthroplasty; specific type of pain – postoperative pain; NSAIDs usage as the main type of adjunctive analgesics were identified. The main exclusion

criteria were: Additional different analgesic techniques; nonhuman species; full text not available online.

We critically appraised the articles using PRISMA statement³ and CASP checklists⁴, and summarised and compared the obtained results.

Overall, five articles meeting the set criteria were identified to be relevant to this review. In particular, we looked at the levels of pain and incidence of opioid-related side-effects as outcome measures for each paper reviewed.

The review established that five different NSAIDs in combination with opioids had been used (Lornoxicam, Parecoxib sodium, Etoricoxib, Tenoxicam, and Celecoxib). All these drugs contributed to varying degrees to postoperative analgesia, however only Lornoxicam showed a significant opioid-sparing effect, thereby decreasing the incidence of opioid related side-effects.⁵

This systematic review shows that so far there is very limited Level 1b evidence⁶ to support a rational choice of NSAIDs as adjuncts to postoperative analgesia after total knee arthroplasty. Consequently, further clinical research is necessary. A particular focus on the effects of Lornoxicam in this context may have merit.

Acknowledgements

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Ratifying the dosage and duration of levobupivacaine infusion by the caudal-epidural route in infants aged three to six months

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The pharmacokinetics of levo-bupivocaine are age-dependent.¹ Current paediatric protocols for caudal-epidural infusions of levo-bupivacaine are derived from bupivacaine-based pharmacokinetic modelling aiming for plasma levels below $2-2.5 \,\mu g/$ ml². Levo-bupivacaine levels have been evaluated following single caudal-epidural boluses³. However, no studies have investigated this in infants less than 6 months with a single bolus followed by an infusion. This phase-II/III clinical trial aims to validate levo-bupivacaine pharmacokinetic modelling in infants aged 3-6months and ensure that toxic levels are not being reached by present protocols of levo-bupivacaine (i.e. bolus followed by an infusion). This would inform clinical practice and dosing for major surgical procedures.

Ethics approval: Northwest Research Ethics Committee(15/ NW/0240) and MHRA (EudraCT 2015-000393-0034). After informed parental consent, 8 infants, aged 3-6 months undergoing bladder exstrophy repair were included. They had a tunnelled caudal-epidural catheter (20G 'Arrow' reinforcedflexi-tip) inserted under general anaesthesia with invasivearterial and central-venous pressure monitoring. Surgery took 6-10 hours: closure of bladder and abdominal wall, anterior pelvic osteotomies and external pelvic fixation. Infants received a bolus of 2.0 mg/kg, 0.25% levo-bupivacaine via caudal-epidural catheter, followed by an infusion of 0.2 mg/kg/ hr 0.125% levo-bupivacaine with clonidine (1.5 µg/ml), initiated after 60 minutes and continued for 48hours. A literature-based levo-bupivacaine and a1-acid glycoprotein(AAG) model was developed to predict the impact of surgical alteration of AAG levels (an acute phase protein) on total levo-bupivacaine concentrations. Blood samples were obtained at predetermined intervals up to 72 hours and total plasma levels of levo-bupivacaine and AAG were analysed. Population pharmacokinetic modelling was carried out to analyse the generated clinical data (total levo-bupivacaine and AAG) using NONMEM7.3 (ICON plc, Dublin, Ireland).

Complete results were obtained from 6-out-of-8 patients. Maximum plasma level of total levo-bupivacaine at 1 hour was 0.7 μ g/ml. (range=0.20-0.7). Maximum total levo-bupivacaine observed at 48 hours was 1.85 μ g/ml (range=0.07-1.85). Serum AAG levels also continued to rise up to 72 hours. But, the simulated unbound levo-bupivacaine levels, based on the current model, suggests that unbound levo-bupivacaine quickly reaches steady state concentrations following the loading dose and is maintained at a constant level of around 0.03 μ g/ml throughout the infusion period (Fig. 3).

This trial validates the pharmacokinetic model and we conclude that in-spite of the increase in total levo-bupivacaine over 48hours, due to the increase in AAG, the unbound levobupivacaine level is maintained at a steady state, well below the predicted toxic levels.



Fig 3. Total-levo-bupivacaine-CtotLBU; unbound-levo-bupivacaine-CuLBU; serum- α 1-acid-glycoprotein-CAAG.

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Elective Hip And Knee Arthroplasty (HAKA) audit looking at anaesthetic technique, postop pain scores, nausea, vomiting, first mobilisation times, patient satisfaction and days until discharge prior to the implementation of an enhanced recovery pathway at Pilgrim Hospital

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Demand is increasing for elective hip and knee arthroplasties. At Pilgrim Hospital, no consensus existed for the preferred anaesthetic technique. The balance is between anaesthetic technique, good post-op analgesia and early mobilisation. The shared goal is ultimately a good patient journey and early discharge. Enhanced recovery pathways for hip and knee arthroplasties are being used in other hospitals nationwide and their effectiveness studied^{1,2,3}. The aim of this audit is to provide evidence of current management and to roll-out an enhanced recovery pathway.

This is a prospective data collection of elective Hip and Knee arthroplasties. Over 11/5/16 to 16/6/16. We included patients receiving Spinals (with or without diamorphine) and general anaesthesia (with or without regional blocks which included femoral, sciatic and/or iliac). We collected: visual analogue pain scores (0–10) in recovery and every six hours for three days; incidence of nausea and vomiting; time until first mobilisation; patient satisfaction and days until discharge. We used a data collection form and 'WebV' electronic system.

Total 52 patients. 28 Hips (7 Revisions). 24 Knees (1 Revision). Average age 70 yrs and ASA 2. For full results see Table 2. Morphine patient controlled analgesia (PCA) was used for 25 patients with similar usage on day 1 of 19 mg average and satisfaction rating of 'good/very good'. Without PCA it was 'good' despite comparatively less oral morphine. Mobilisation and discharge was delayed for 1) Knees with PCA vs oral morphine (not apply to hips) 2) Hip and knees with blocks. With blocks post-op analgesic requirements were higher with higher pain scores and worse patient satisfaction. Pain, mobilisation and discharge with diamorphine in spinals is comparable to those spinals without diamorphine but incidence of nausea is more with diamorphine. Primary vs revisions: Hip mobilisation and discharge is comparable but for knees is longer for revisions.

There are some limitations such as sample size. Pain scores are subjective and occasionally retrospective which limits their comparison. PCA dose documentation varied. There were three post-op complications reducing weight of discharge data. Experience of operator for regional block not collected. Incidence of Urinary retention not collected.

Table 2 Summary of findings.	
Location	Anaesthetic room: 10
	Theatre: 6 (pre-bypass: 3)
Onset time	<30 min: 13; >30 min: 3
Cardiac arrest needing CPR	1
Decision to continue	Postponed: 10
with surgery	Proceeded: 7
Re-operation time	4 days-14 months
90-day survival	100%
Allergy clinic review time	7 days – 8 months

Currently no set standardised management for these cases at Pilgrim. This data supports that 1) Blocks should be considered with caution 2) Spinals without diamorphine should be done 3) Avoid use of PCA in primaries but may benefit in revisions. Action plan from audit was to discuss and implement a standardised anaesthetic practice for elective hip and knee.

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Incidence and outcome of anaphylaxis in cardiac surgical patients – should we proceed to cardiopulmonary bypass and complete surgery?

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Anaphylaxis is defined as a severe, potentially life threatening systemic hypersensitivity reaction.¹ The incidence of peri-operative anaphylaxis is approximately 1:10,000-20,000 anaesthetic procedures.² Anaphylaxis in patients with cardiac disease is likely to pose added risk of adverse outcome. Cardiac surgery is unique because there is the opportunity for immediate cardio-respiratory support using bypass (CPB) following an anaphylactic event. One could propose that all cardiac surgical patients undergoing anaphylaxis should be supported with CPB until stability is established. However, a secondary decision to then proceed to completion of surgery is more difficult. The sixth National Audit Project (NAP6) is collecting information on perioperative anaphylactic events in order to make recommendations to improve patient care.³ The aim was to investigate the incidence and management of anaphylaxis in cardiac surgical patients.

Retrospective case note review of cardiac surgical patients reported to have had an anaphylactic reaction over a period of 20 years (1997–2017). Data collected included age at time of event, gender, cause (after allergy testing), type of surgery, location (Anaesthetic room or theatre), onset time, need for CPR, decision to continue with surgery, time for reoperation, 90-day survival, time taken to be reviewed in allergy clinic. 17 peri-operative anaphylaxis incidents were reported amongst 17589 patients (0.1%). Most (76%) occurred within 30 minutes of induction of anaesthesia with 7 (41%) of the 17 proceeding to completion of planned surgery.

We found a greater incidence of anaphylaxis in our cardiac patients compared to the general anaesthetic population. However, it will be interesting to see the results of NAP6, because this may be due to differences in reporting. We are unaware of any consensus or recommendations for continuing to cardiac surgery following anaphylaxis. Some, that occurred either pre- or during bypass, were postponed whilst others (41%) proceeded to completion of intended operation – this 41% having good outcomes. The delay in reoperation in some of those postponed was very prolonged. The reasons for postponement were not investigated. However, management of anaphylaxis for patients undergoing cardiac surgery pose interesting dilemmas, which need further review.

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A comparison of ventilatory efficiency parameters from Cardiopulmonary Exercise Testing (CPET) as predictors of mortality following major abdominal surgery

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 V_E/VCO_2 at anaerobic threshold (V_E/VCO_2 AT) is an important preoperative CPET variable that can identify patients at increased risk of mortality across different surgical populations ^{1,2}.

 V_E/VCO_2 slope (measured from start of exercise to the respiratory compensation point) theoretically offers an advantage over V_E/VCO_2 (measured at a single point in time which may itself be difficult to identify reliably) and has demonstrated clinical utility in heart failure prognostication and in valvular heart disease.³ There are no studies to date investigating the use of V_E/VCO_2 slope in preoperative assessment and patient outcomes following major surgery. This study compares measured V_E/VCO_2 slope with V_E/VCO_2 AT in a cohort of patients undergoing major abdominal surgery and their association with postoperative mortality.

Routine preoperative CPET performed in 917 surgical patients (M/F 565/352, mean age 69.1 yr) at our institution between Feb 2012 and Dec 2014, were retrospectively examined to ascertain the following parameters: V_E/VCO_2 slope between start of exercise and the respiratory compensation point and V_E/VCO_2 AT. Survival data was obtained from the Demographic Batch Service (DBS) and Trust clinical databases. Patients who did not proceed to surgery were excluded from the analysis.

There were 41 (4.5%) deaths at 90 dy and 133 (14.5%) at 1 yr. For the V_E/VCO₂ slope at a cut-off > 42 the risk of 90 dy and 1 yr mortality was OR (95% CI) 4.8 (2.2,10.7), p < 0.0005 and 2.5 (1.3,4.5), p=0.004 respectively whilst VE/VCO2 AT > 42 was non-significant for mortality at both 90dy and 1yr. For a cut-off > 34 the OR was significant for both V_E/VCO₂ AT and V_E/VCO₂ slope at both 90dy and 1yr but V_E/VCO₂ slope demonstrated a higher OR. At 90dy this was OR (95% CI) 2.8 (1.4,5.4), p=.002 for V_E/VCO₂ AT and OR (95% CI) 4.1 (2.1,7.7) p<0.0005 for V_E/VCO₂ slope.

 $V_{\rm E}/VCO_2$ slope potentially offers advantages over $V_{\rm E}/VCO_2$ AT in identifying patients at increased mortality risk following major abdominal surgery. $V_{\rm E}/VCO_2$ slope over the whole exercise should be measured alongside $V_{\rm E}/VCO_2$ AT in patients undergoing preoperative CPET.

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Post-operative serum lactate measurement and pre-operative fitness as determined by CPET as predictors of mortality after major elective abdominal surgery

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It has been demonstrated that lactate clearance in the first 24 hours after surgery is a strong independent predictor for major postoperative complications¹. Cardiopulmonary exercise testing (CPET) has been shown to be a robust and reliable tool for predicting perioperative outcomes in a number of major surgical cohorts and is now an established practice in the management of major surgery patients ^{2,3}. This study examines the effect that pre-operative fitness as determined by CPET and post-operative lactate have on the risk of post-operative mortality.

Contemporaneous CPETs performed in our institution between July 2007 and Jan 2014, in patients undergoing major elective abdominal surgery, were matched with patient survival. During this time period 1078 patients (M/F 707/371, mean age = 69.3 yr) underwent pre-op CPET and proceeded to surgery and were cared for in a level 2 or level 3 setting. As part of standard peri-op care serum arterial lactate is routinely measured in our institution to help guide therapy. Routinely acquired arterial serum lactate measurements during the postoperative period were retrospectively collected from the automated blood gas analysers (Radiometer ABL850) and analysed for the 48 hours following the completion of surgery. End of surgery times were extracted from the RECALL Anaesthesia Management System, to time the lactate measurement period. All patients undergoing liver surgery were excluded because of the alteration in lactate metabolism.

In multivariate analysis, hyperlactaemia (mean lactate > 2 mmol/L) in the first 48 hrs and V_E/VCO₂> 34 were both significantly associated with risk of mortality at 90dy. For mean lactate >2 mmol/L the odds ratio (95% CI) was 3.23(1.94,5.36), p<0.005 and for V_E/VCO₂ >34 it was 2.07(1.24,3.45) p<0.06. For the combined hyperlactaemia (mean lactate > 2mmol/L) with V_E/VCO₂ >34 group there was a four-fold increase in odds of mortality at 90dy, OR (95% CI) 3.92 (2.20,6.96), p<0.005. Similar results were demonstrated for hyperlactaemia over the 1st 24 hrs with the same CPET variable.

Post-operative hyperlactemia in the first 48 hours after surgery in combination with abnormal CPET appears to be associated with mortality disadvantage and we believe this is the first study to examine CPET with hyperlactemia in the post-op setting.

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Exclusion of the elderly and the use of patient related outcomes in anaesthetic research: a systematic review (The APPROPRIATE study)

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Mortality after major surgery is approximately 4%, which translates to over 9 million deaths per year worldwide¹. Frail patients are at a greater risk of complications following anaesthetic interventions². Research suggests a propensity to exclude the elderly from clinical trials³. There are currently no systematic reviews of the anaesthetic literature in this area. The European Charter for Older People in Clinical Trials reiterated the need for such investigation and the need to include outcomes relevant to older people in future studies⁴.

The aim of this systematic review was to assess exclusion of the elderly and measurement of relevant outcomes in anaesthetic research. Randomised controlled clinical trials (RCTs) (apart from Phase I and II drug trials), featuring an anaesthetic intervention, published in one of ten major anaesthetic/general medical journals were included. These journals were selected by Impact Factor, in the five-year period of 2012-2016, (BJA, Anesthesiology, Pain, Anaesthesia, Anaesthesia and Analgesia; N Eng J Med, Lancet, JAMA, BMJ and Annals of Int Med). Outcomes included proportion of RCTs, which directly or indirectly excluded the elderly, proportion which measured one or more Patient Reported Outcome Measures in the areas of: quality of life, functional status, or requirement for care or dependency peri-interventionally. Trials were identified through EMBASE and MEDLINE with validation from a qualified librarian. Two independent experts reviewed articles. A third independent reviewer resolved any disagreements.

This review included 62 RCTs. The proportion of trials excluding the elderly by direct (17.7%) and/or indirect (19.4%) methods was 30.6% (19 studies). One or more older person appropriate PROMs were investigated in 22.6% (14 studies) of trials. Quality of life was reported in 9.7% (6 studies), requirement for care or dependency measured peri-interventionally in 9.7% (6 studies), functional status measured in 22.6% (14 studies). In studies where it was deemed advantageous by the research team, a validated delirium tool was included as an outcome in 11.5% (6 of 52 studies). Frailty was rarely assessed.

A proportion of relevant RCTs in anaesthesia excluded the elderly. Furthermore, the investigation and reporting of outcomes and parameters that are considered important to older people were omitted from the majority of these trials.

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Fluid balance in peri-operative and critical care staff

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Dehydration is known to have detrimental effects on cognitive function and physical performance, as well as increasing the long-term risk of hypertension, coronary heart disease and stroke.¹ A number of studies have shown inadequate nutritional and fluid intake in doctors.^{2,3} There is increasing evidence and interest in the importance of healthcare staff wellbeing and its implications for patient safety.⁴

A prospective, observational cohort study was conducted on medical and nursing staff working in peri-operative and critical care medicine at a tertiary teaching hospital over a 24 hour period. Fluid balance charts were distributed to staff who were asked to complete these for the duration of their shift. Using 2500 mls as the recommended daily fluid intake¹ and average waking hours as 17,⁵ 147 mls/ hour was used as the standard with which to compare our results. Analysis was conducted using an unpaired Student t test.

One-hundred-and-thirty-five fluid balance charts were distributed and 79 completed, giving a response rate of 58%. Only 3.8% of staff met the recommended fluid intake (n=3). The mean fluid intake was 76 mls/hr (\pm SD 32). On-call staff had a significantly lower fluid intake than those on normal shifts (24 vs. 78 mls/hr (p=0.005)). Night staff had a higher fluid intake than day staff (93 vs. 72 mls/hr (p=0.043)). Forty-seven percent of drinks consumed were caffeinated (\pm SD 35%). Staff passed urine 2.2 times per shift (\pm SD 1.0).

This study found inadequate fluid intake amongst most medical and nursing staff. Study participants suggested reasons such as lack of time, limited availability of drinking facilities and staffing shortages. In spite of the small sample size, with over 96% of staff not meeting the recommended fluid intake, our results have potential implications for staff and patient safety. Dehydrated staff may be unable to perform as well cognitively and risk potentially detrimental effects on their short and long-term health. This study adds weight to existing research and highlights the need for fluid promotion among healthcare staff.

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Magnesium sulphate as an adjuvant to fentanyl for attenuation of intubation response

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This prospective, randomised, double blind study aimed to analyse the impact of magnesium sulphate $(MgSO_4)$ as an adjuvant to Fentanyl to depress the intubation response.

Sixty female patients of ASA I and II undergoing elective mastectomy were randomly allocated to two groups. The study group given 30 mg/kg of MgSO₄ diluted to 20 ml i.v. before induction over ten minutes and control group 20 ml of NaCl 0.9%. The heart rate (HR), systolic blood pressure (SBP), diastolic (DAP) and mean arterial (MAP) pressures were recorded as baseline, one minute after the drug infusion, at induction, intubation, and at one minute intervals up to five minutes. Patients were induced with propofol 1% (up to 2 mg/ kg), fentanyl (2 mcg/kg) and atracurium (0.5 mg/kg). Tracheal intubation was performed on disappearance of single twitch after atracurim administration. Serum MgSO₄ levels in the study group were recorded before and two hours after giving MgSO₄.

A clinically significant rise in HR (mean +17.23%) was observed in the study group after receiving MgSO₄ before induction. The control group (fentanyl only) showed significant increase in SBP (13.3%), DBP (9.3%), MAP(12.89%), and HR(13.86%) after intubation. Administration of MgSO₄ and fentanyl significantly reduced the haemodynamic response as observed in study group SBP (-9.25%), DBP (-14.4%), MAP (-10.4%), HR (-1.3%) (.p<0.001). The values did not rise above the baseline at any point of observation. After two hours, the magnesium levels showed a significant rise from baseline levels (mean 16.4%), but remained within normal limits.

 $MgSO_4$ at a dose of 30 mg/kg significantly attenuates the haemodynamic response to laryngoscopy and intubation when administered before anaesthesia induction. This dose can be safely used as an adjuvant in rapid sequence inductions on patients in which haemodynamic changes would be detrimental, such as head injury or ocular injuries.

Serial holter recordings in non-cardiac surgery patients reveal postoperative autonomic impairment within 48 hours

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Baroreflex impairment is independently associated with excess post operation morbidity and prolonged hospitalisation.¹ This suggests a mechanistic role for autonomic dysfunction in determining perioperative outcome. However, the time course over which cardiac autonomic function changes perioperatively remains unclear.

Elective surgical patients at higher risk of myocardial injury according to VISION criteria² (n=119 patients) were recruited in a prospective single-centre observational study (REC16/LO/ 0635). Serial electrocardiographic (ECG) holter monitoring (Spacelabs Lifecard CF monitor, Spacelabs Healthcare) was undertaken preoperatively, 24 h and 48 h after surgery. We recorded ECG, non-invasive blood pressure and respiratory rate for 10 minutes in the lying position before repositioning the patients at 45 degrees and repeating the tests in order to assess postural autonomic changes. Cardiac autonomic function was assessed using time and frequency domain heart rate variability analyses (Pathfinder Software, Spacelabs Healthcare; Nevrokard aHRV Software). High frequency (HF) domain was used as a marker of cardiac parasympathetic activity and low frequency (LF) domain was used as an indicator of baroreflex activity.³ For each patient, we assessed changes in autonomic function perioperatively over time and in relation to position (repeated measures ANOVA with post hoc Tukey-Kramer tests).

Figure 4 shows the serial perioperative changes for heart rate, HF and LF (mean and 95% confidence interval). There was a significant increase in heart rate at 48h compared to the

preoperative and 24h heart rate in both the lying and 45 degree position. Low frequency and high frequency both significantly decreased after surgery, but only after 24h. Our study shows that a reduction in cardiac vagal modulation develops by 48h after surgery, consistent with our previous data.⁴ Loss of LF suggests the development of baroreflex dysfunction. These data suggest that autonomic impairment is acquired in the recovery period after surgery, and therefore potentially modifiable (e.g. with targeted mobilization⁵ and/or other therapeutic interventions.⁶



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Feasibility of abbreviated penicillin delabelling in the elective surgical patients: the PADLES study – an early report

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Penicillin allergy is the most commonly reported drug allergy, with up to 20% of patients carrying this label. When tested, fewer than 10% of such patients were found to be allergic¹. Incorrect penicillin allergy labels are potentially harmful, with the label increasing the risk of MRSA and C. *difficile*, longer hospital stays, and mortality ¹. Testing for penicillin allergy involves skin testing (\pm serum testing), followed by an oral challenge test when these are negative ². However, increasing evidence suggests that patients with a 'low risk' history can safely have a direct oral challenge ². If this is tolerated without incident, they are 'de-labelled' and advised that they can receive penicillin in the future. We sought to establish the feasibility of offering this abbreviated testing pathway to 'low risk' elective surgical patients who require penicillin for their surgery.

Patients who self-reported a penicillin allergy during routine pre-assessment were screened for eligibility using a questionnaire. Patients with a 'low risk' and meeting the inclusion criteria were offered to attend on a separate day for delabelling with a graded oral amoxicillin challenge (or the index penicillin to which they were allergic). If there were no signs of allergy within the two hours of completing the challenge, patients went home with a 3-day course of amoxicillin, after which they were contacted to rule out any delayed reactions before being formally de-labelled. The patient, surgeon and GP were informed of the results, and the hospital electronic records updated. The notes of patients were reviewed after surgery to assess which antibiotic had been administered intra-operatively.

Penicillin allergy was self-reported in 80 patients, with fifteen eligible for inclusion. To date, 10 of the eligible group have received the graded oral challenge and none has had any immediate or delayed reactions to the amoxicillin. Six of these patients proceeded to have uneventful surgery with penicillin prophylaxis, with four still waiting. Of the 65 ineligible patients, reasons for ineligibility included: high risk symptoms (36/65), did not require penicillin for surgery (20/65), allergic reaction within fifteen years (16/65), declined testing (15/65), insufficient time for testing prior to surgery (7/65), and medical condition preventing inclusion (3/65).

Our preliminary data demonstrates that patients allergic to penicillin can be identified, risk-stratified then de-labelled using an abbreviated testing pathway prior to their planned surgery. These patients then go on to receive penicillin for their surgery, rather than broad spectrum alternatives. This abbreviated pathway has the potential to enable large-scale 'de-labelling' to benefit individuals, and improve the wider antimicrobial stewardship.

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Magnesium sulphate significantly reduces isoflurane and vecuronium bromide requirements in laparoscopic cholecystectomies

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The anesthetic effect of magnesium sulphate (MgSO₄) is related to several mechanisms, such as antagonism of N-methyl-Daspartate receptors in CNS and calcium channels at presynaptic nerve terminals, leading to decrease stress response by reducing catecholamine release¹ and inhibition of acetylcholine release at motor nerve terminals², respectively.

We conducted a prospective, randomized, placebocontrolled, double-blinded study to investigate the isoflurane and vecuronium requirement in patients who underwent laparoscopic cholecystectomy and received $MgSO_4$ by two techniques.

Sixty patients of similar demographic variables who underwent laparoscopic cholecystectomy surgery were randomly divided into three groups. Before induction of anaesthesia, the MgSO₄ bolus group (MB) received MgSO₄ 50 mg/kg i.v. as a bolus followed by continues infusion of 0.9% NaCl. MgSO₄ bolus plus MgSO₄ infusion group (MI) received bolus MgSO₄ 50 mg/kg i.v. followed by 10 mg/kg/h i.v. continuous infusion. The control group (NS) received the same amount of NaCl 0.9% as bolus and infusion. General anaesthesia was induced by standard technique using fentanyl, thiopentone and vecuronium 0.1 mg/kg was administered before intubation. Top up doses of vecuronium 0.025 mg/kg were given under neuromuscular monitoring when the train-of-four count was 2 or more. Anaesthesia was maintained with 33% oxygen, 66% nitrous oxide, 0.5-2% isoflurane through the closed circuit with controlled ventilation to maintain normocapnia. Isoflurane was titrated to maintain bispectral index (BIS) values of 40-60. After an appropriate equilibration period, baseline minimal alveolar concentration (MAC) was determined and subsequent readings were noted at set intervals. Total intraoperative consumption of vecuronium was recorded at the end. Data was analyzed by using one way ANOVA (mean \pm SD).

NS isoflurane concentration $(1.24 \pm 0.14\%)$ was recorded significantly higher (at all time points) during pneumoperitoneum compared to MB ($1.01 \pm 0.18\%$) and MI ($0.84 \pm$ 0.49%) groups (p<0.01) to maintain haemodynamic parameters within \pm 20% of preinduction values. The requirement of isoflurane was found less in MI, compared to MB but was not statistically significant. Mean dose of vecuronium required in MB (6.65 \pm 0.988 mg) and MI groups (5.95 \pm 0.759 mg) were found to be lower than the NS group (6.95 \pm 0.945 mg). Statistically, a significant difference was noticed in the dose requirement between NS and MI groups (p=0.003) and also between MB and MI groups (p=0.045). No statistically significant difference was found between NS and MB groups (p=0.548). None of the patients in the study had delayed neuromuscular reversal.

Both MgSO₄ bolus and bolus followed by infusion significantly reduced the isoflurane and vecuronium requirement without haemodynamic compromise and delayed neuromuscular reversal. Thus, use of MgSO₄ appears to be safe in this setting.

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Trends in obesity amongst patients undergoing general anaesthesia at Great Ormond Street Hospital for Children, London

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The prevalence of obesity in children is increasing worldwide.¹ Obese children are more likely to suffer comorbidities² and are at greater risk of perioperative complications³. Childhood obesity poses an increasing burden to healthcare resources and screening for obesity may help target these resources where they are most needed. This study aims to establish trends in the burden of paediatric obesity on general anaesthesia services, at a specialist children's hospital, over the past decade.

We performed a retrospective review of data obtained from the Patient Information Management System, including all patients aged 4–18 years undergoing general anaesthesia at Great Ormond Street Hospital, between 2006 and 2016. Variables included date of birth, date of procedure, gender, height and weight. Body Mass Index (BMI) was calculated using the standard equation. UK 1990 growth chart BMI data was obtained under licence from the UK Medical Research Council⁴. A linear regression model was constructed adjusting BMI for age, sex and year of measurement. The primary outcome was the percentage of obese patients, defined as a BMI above the 98th centile.⁴

The institutional clinical audit and research governance departments deemed that the study did not require local research ethics committee approval and it was registered as a service evaluation (registration number 2055). All analyses were performed using R software version 3.3.2.

A total of 73399 patients aged 4–18 years underwent general anaesthesia from 1st January 2006 to 24th November 2016, of which height and weight data was available for 55170. After data cleaning 35977 patients were included in the final analysis, of which 4624 were obese (12.9%).

This study demonstrates no significant change in the prevalence of paediatric obesity over the 11 year period from

January 2006 to November 2016 at Great Ormond Street Hospital, London. Despite this there was still a significant proportion of patients that were obese (12.9%) which represents an immediate perioperative risk³, as well as a longterm health and economic burden for individuals and healthcare services. Improving recognition of childhood obesity may enable the reduction of perioperative risk and the potential to intervene with the involvement of specialist obesity services.

We recommend: (1.) Introduction of a care pathway to identify obesity in patients prior to general anaesthesia; (2.) Development of a perioperative protocol for the management of the obese child undergoing general anaesthesia; (3.) Introduction of a specialist obesity service.

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Monitoring of neuromuscular blockade during general anaesthesia

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Accidental awareness under general anaesthesia (AAGA) is an uncommon but particularly distressing complication, with potentially long-lasting psychological consequences. Over 400 reported cases of AAGA were reported during the fifth National Audit Project, with a projected incidence of 1:136000 general anaesthetics.¹ However, 97% of reported cases of AAGA were associated with the use of neuromuscular blocking drugs (NMBDs), an incidence of 1:8000¹. Around one-fifth of these reported cases were at emergence with all patients experiencing residual neuromuscular blockade. Failure to use a peripheral nerve stimulator was seen as causal or at least contributory in half of these cases. The 2015 updated guidance from the Association of Anaesthetists of Great Britain and Ireland (AAGBI)² stated that a peripheral nerve stimulator must be used when a NMBD is given, as part of the minimum standards of monitoring during general anaesthesia.² We aimed to explore the current use of NMBDs, nerve stimulators and reversal agents during general anaesthesia in a UK teaching hospital.

A retrospective anaesthetic chart review of patients receiving surgery under general anaesthesia was undertaken at Leicester Royal Infirmary. Information collected included patient characteristics, NMBD used and timings, use of a nerve stimulator and reversal agent.

Twenty nine patient anaesthetic charts post general anaesthetic and neuromuscular blockade drug have been reviewed to date. 11 male, mean age 50.8, 4 emergency procedures (14%) 25 elective procedures (86%), ASA 1-3. Atracurium was used in 62% of procedures and 87% of patients had a documented reversal agent administered. 14 charts (48%) had documented use of a peripheral nerve stimulator or neuromuscular monitoring peri-operatively. A Consultant Anaesthetist was present in all cases and trainees were also present in approximately half of the procedures. The documented use of neuromuscular monitoring showed no relationship with level of anaesthetist present.

Neuromuscular blockade drugs are commonly used during general anaesthetic and increase the risk of accidental awareness under general anaesthesia. Although monitoring can reduce this risk, use has only been documented in 50% of cases by anaesthetists of varying experience. Data collection is ongoing and we plan to investigate any potential barriers or difficulties in our local hospital to using neuromuscular monitoring.

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Microvascular function in healthy volunteers; a comparison of manually and automatically derived measurements

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Microcirculatory dysfunction plays a significant role in the pathophysiology of critical illness, including sepsis, haemorrhage and cardiogenic shock. Studies have used video microscopic measurements of the sublingual microcirculation in acute illness, but the clinical utility of these techniques are limited by the need for time-consuming analysis that precludes near-patient data interpretation. The newest video microscopes use Incident Dark Field (IDF) illumination technology (see below) with automated analysis. However the automated analysis has not been validated and there are no data on normal ranges in healthy individuals. This limits the potential application of IDF video microscopy for microcirculation research.

This study aims to examine the feasibility and accuracy of measurement of sublingual microvascular function in the awake individual establish the summary statistics of different sublingual microvascular measurements and compare these measurements in three age groups; 18–34 yrs, 35–54 yrs and over 54 yrs. Additionally, this study will correlate the automatically derived measurements of microcirculatory function in comparison to the current gold-standard of manual analysis.

An observational study of 150 healthy volunteers, which will include the recording of basic physiological data, medical and drug history, followed by an assessment of the sublingual microvascular bed using CytoCam incident dark field microscopy to measure total vessel density (TVD), perfused vessel density (PVD), and microvascular flow index (MFI). Analysis using current gold standard manual analysis with automated analysis using CytoCam Tool 1.7 (Braedius Medical BV) Analysis plan: (a.) Computation of summary statistics of TVD, PVD, and MFI to determine normal ranges for both manual and automated analysis methods at the population level as well as age-related subgroup level (18-34 yrs, 35-54 yrs and 55 yrs and over). (b.) Estimation of correlation between automatically and manually derived values of TVD, PVD, and MFI within each subject. (c.) Comparison of mean TVD, PVD, and MFI between the age-related subgroup (18-34yrs, 35-54 yrs and 55 yrs and over).

Progress: This study has currently recruited 91 of 150 subjects. The procedure of measurement has been found to be well tolerated, with no subjects withdrawing from the study once enrolled. Further, it has been possible, following 2 days of intense work, to train a further member of the team to make reliable, high quality recordings, demonstrating the scope for training those new to the technique to use it in the clinical setting. We look forward to producing full results in the near future.

Orexinergic tone affects survival in sepsis in rat

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Orexinergic (OXergic) system contributes to cardiovascular defense system which is attenuated in OX knockout and OX neuron-ablated animals such as OX/ataxin-3 transgenic (OX/ AT3-TG) rats revealing OXergic neuronal degeneration and decline in OXA level¹. It has also been reported that degeneration of OXergic neurons occurs during sepsis¹. Thus, the decline of OXergic activity may partly be involved in the pathophysiology of sepsis. In the present study, we have determined whether lipopolysaccharide (LPS) reduces OXA content in the brain and also whether deficiency in the OXergic system affects survival from sepsis in rats.

After approval of our protocol by our University animal ethics committee, OX/AT3-TG and ordinary Sprague-Dawley (SD) rats weighing 250-350g were used in this study. Lipopolysaccharide (LPS) 10 mg/kg was ip given to each SD rat (n=28, Group SD) and OX/AT3-TG rat (n=14, Group TG). Other SD rats (n=7) were given ip saline as a Control group. Then, survival analysis was performed on the rats over a period of 3 days; surviving rate was calculated. After the above experiments, all surviving rats were decapitated, the brains quickly removed and the cerebral cortex, the hippocampus, the hypothalamus and the pons were dissected from their internal structures and then immediately sonicated in 10×brain tissue weight of Krebs-Ringer bicarbonate buffer solution. The supernatant was collected and stored at -70°C until OXA extraction was performed. OXA in the samples was quantified using ELISA kits. The data are expressed as means±SD. Where appropriate, statistical analysis was performed by one way ANOVA followed by the Student-Newman-Keuls test or $\chi 2$ test. A p<0.05 was considered significant.

All rats in group Control and 16 of 26 rats (61.5%) in group SD survived while only 3 of 14 rats in Group TG (21.4%) survived (p<0.05). LPS significantly reduced OXA content in the pons, and OXA/AT3-TG rats had a significantly lower OXA contents (Table 3).

As OXergic system has been reported to contribute to cardiovascular defense system, significantly lower survival may be due to weakened defense system in OX/AT3-TG rats. In addition, similar to previous reports, LPS significantly reduced OXA contents in the pons containing the locus ceruleus. Therefore, changes in OXergic activity may contribute to the pathophysiology of sepsis. 0.03, LOA -0.16, 0.21 for intra-observer variability for RV-MPI measurement. There were no changes in RV-MPI over the study period (Friedman's test, p=0.78). On pooled analysis, there was weak negative association between RVEF and RV-MPI (r=-0.29, p=0.02, Spearman's) which

Table 3 OXA content (pg/mg tiss	ie) in each brain region	ı. (\$: p<0.01 vs Control, #: p<0.0	1 vs SD).

Group (n of survival rats)	Control (7)	SD (16)	TG (3)
Hypothalamus	6.15±2.85	6.11±1.67	1.24±0.47\$#
Cerebral Cortex	1.13 ± 0.41	1.12±0.18	0.39±0.12\$#
Hippocampus	1.72±1.01	1.79±0.37	0.82±0.12
Pons	4.10±1.21	2.92±0.38	0.62±0.25\$#

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Right Ventricular Myocardial Performance Index as an assessment of right ventricular function following lung resection

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Right ventricular (RV) function deteriorates following lung resection and has been shown to be associated with postoperative complications and long-term morbidity. Using cardiovascular magnetic resonance (CMR) imaging, a reference method for assessment of RV function, our group has demonstrated a deterioration in RV ejection fraction (RVEF) in this patient group. Despite being commonly used in clinical practice, trans-thoracic echocardiographic (TTE) assessment of RV function is challenging, with regional geometric parameters often used to reflect global RV function.

RV-Myocardial performance index (RV-MPI) is the ratio of RV isovolumetric time to RV ejection time, and is described as a nongeometric index of global RV function. RV-MPI has been validated against RVEF in other clinical conditions and has been used in the prognostication of patients with pulmonary hypertension and congenital heart disease. Colour-coded tissue Doppler (CC-TD) analysis is a novel method for offline assessment of tissue velocities and can be used to measure MPI. We investigated changes in RV-MPI over time and sought to compare CC-TD derived RV-MPI with RVEF obtained by CMR.

With ethics approval and informed consent, 27 patients undergoing lung resection by thoracotomy underwent serial TTE and CMR imaging; pre-op, on post-operative day (POD) 2 and at 2-months. CC-TD analysis was performed offline by placing a region of interest at the free wall of the tricuspid annulus from the apical 4-chamber view (Echopac, GE healthcare). RV-MPI was determined from the dual analysis of randomised and anonymised images. Bland-Altman analysis was used to assess agreement between observations. Changes in RV-MPI over time were assessed using Friedman's test. Association between RV-MPI and RVEF obtained contemporaneously from CMR imaging was made using Spearman's correlation.

Bland-Altman analysis showed bias 0.00, limits of agreement [LOA] -0.19, 0.20 for inter-observer and bias

was lost when assessed at individual time points (p>0.06 for all).

Adequate images for RV-MPI measurement were obtainable in all patients. Bland-Altman analysis showed acceptable inter- and intra-observer variability for CC-TD analysis of RV-MPI. Although in small numbers, CC-TD derived RV-MPI was poorly associated with RVEF in this study and as such cannot be advocated as a surrogate measure of RV function in patients undergoing lung resection.

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Caspase-1 and epidural-related maternal fever

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Epidural-related maternal fever (ERMF) occurs in ~20% labouring women, and is associated with more materno-fetal obstetric intervention [1]. The origin of ERMF is not infectious, but remains obscure. We hypothesized that bupivacaine promotes ERMF by modulating cytokine release in leukocytes through mitochondrial injury activating the NLRP3-inflammasome/caspase-1 complex [2], the latter of which also regulates secretion of anti-pyrogenic interleukin-(1)-receptor antagonist (IL-1ra) [3].

Metabolic activity (Oxidative phosphorylation (OXPHOS), glycolysis), a sensitive indicator of inflammation being activated, were measured (respirometry; Seahorse XF96) in NRLP3-/- or null THP-1 monocytes exposed for 4 h to bupivacaine (5-10 μ M) and/or plasma from labouring women (labour plasma). Caspase-1 activity and intracellular IL-1ra were quantified (flow cytometry) in mononuclear leukocytes (MNF) obtained from labouring women, prior to, and 4 h after, bupivacaine (Fig. 5). Plasma IL-1ra was also measured before, and 4 h after, epidural or alternative analgesia.



Fig 5. Temperature during early phase of epidural analgesia, as measured serially (oral) over 4h. Mean values (95%CI) shown. Asterisk denotes p<0.001. B. Activated caspase-1 fluorescence in presence/ absence of bupivacaine in CD3+ cells. Nigericin 10 μ M served as a positive control. Graph shows summary data for CD3+ caspase-1 fluorescence (% cells activated).

Maternal temperature increased $(0.2\pm0.1^{\circ}C; p=0.003)$ only after 4h epidural analgesia, with ERMF subsequently recorded in 7/38 women (18.4%). Bupivacaine did not alter OXPHOS in NRLP3-/- cells, or reverse ~75% suppression of OXPHOS/ glycolysis on exposure to labour plasma (n=5), suggesting bupivacaine is not injurious to mitochondria/pro-inflammatory. Caspase-1 activity was measurable in 14% fewer MNF cells (95%CI:8-20); n=9) obtained from labouring women after 4h incubation with bupivacaine, which also increased intracellular IL-1ra by 25 \pm 9% in MNF (p<0.001; n=8). Plasma IL-1ra increased by 38 \pm 5% over 4h in women without an epidural (n=6), but not after epidural analgesia (n=17).

Bupivacaine reduces caspase-1 activity in circulating leukocytes and IL-1ra secretion. Reduced circulating levels of anti-pyrogenic IL1-ra, rather than pro-inflammatory inflammation, may promote ERMF

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Effect of perioperative epidural insertion on disease recurrence following renal cancer surgery

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Surgery facilitates cancer progression via the immunosuppressive effects of the surgical stress response, dispersion of micro-metastases, and VEGF-mediated angiogenesis.¹ Regional anaesthesia inhibits this surgical stress response, reduces pain, and has a direct anti-cancer effect.² The aim of this study is to ascertain whether there is any difference in cancer recurrence rates in patients undergoing radical nephrectomy for renal cell carcinoma receiving epidural analgesia plus a general anaesthetic, compared to general anaesthesia alone.

We analysed single surgeon/single centre data collected over 12 years, and divided patients into two groups; those with a perioperative epidural, and those without. We compare time to radiologically detected recurrence during standard followup. We consider surgical tumour characteristics and blood transfusion rates to identify any significant confounders.

We included 471 patients; 193 in the epidural group, and 278 in the non-epidural group. The mean age of patients in the epidural group was 66, versus 65 in the non-epidural group. Median stage of cancer was 1B in both groups, with mean length of follow up 33 months in the epidural group versus 38 months in the non-epidural group. There were 44 cases of recurrence in the epidural group [23%]; versus 76 cases of recurrence in the non-epidural group [27.3%]; Sub-hazard ratio (SHR) of 0.53 (95% CI 0.24 – 1.09, p 0.08). Mean time to recurrence was 12.8 months in the epidural group, versus 17.1 months in the non-epidural group, sight patients received blood transfusion in the epidural group. SHR for blood transfusion was 0.82 (95% 0.18 - 3.7).

There is a reduced cancer recurrence rate in the epidural group, SHR 0.53, that approaches significance, We believe epidural anaesthesia may be protective against renal cancer recurrence; however, larger, national data sets are needed.

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Oxygen metabolism in malignant hyperthermia susceptible skeletal muscle and the effects of static halothane exposure

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Individuals susceptible to Malignant Hyperthermia (MH) may undergo potentially fatal hypermetabolic responses following exposure to volatile anaesthetics and/or depolarizing muscle

relaxants. A link between MH susceptibility and potential impairment in oxygen metabolism suggests the possibility of chronic mitochondrial dysfunction. Here we evaluated mitochondrial function in skeletal muscle biopsies after in vitro contracture test (IVCT) from MH susceptible (MHS) and nonsusceptible (MHN) individuals, by measuring oxygen consumption rate as flux control ratios (FCR) using the Oroboros Oxograph-2k analyzer. Biopsy samples were permeabilized with saponin and subjected to a protocol adapted for high resolution respirometry^{1,2}. Samples taken before and after static halothane IVCT were assessed for differences in FCR for each mitochondrial complex state. Compared with MHN samples, human MHS samples showed significant activity reduction in complex II, likely the result of mitochondrial damage caused by chronically elevated resting calcium previously reported in MHS muscle³. Halothane exposure during IVCT significantly increased FCR in complex II and the max electron transport system (ETS) state of MHS muscle only (Fig. 6). Based on these data we conclude that there is clear evidence of altered oxygen metabolism in MHS skeletal muscle mitochondria, which we hypothesize to be a result of chronic mutant RYR1 induced increases in cytoplasmic Ca²⁺, supporting a connection between MH susceptibility and mitochondrial dysfunction.



Fig 6. FCR comparison between MHN (n=30) and MHS (n=20) in 6 respiratory states, generated after normalizing oxygen consumption rates to complex IV activity. Significant comparisons are annotated with an asterisk (p<0.05). Error bars are \pm 1 SE.

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The association between intraoperative driving pressure and outcome following one lung ventilation

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Lung protective ventilation (LPV) with low peak inspiratory pressures (Ppeak) and high positive end expiratory pressure (PEEP) is associated with improved outcome and widely accepted as best practice with regards to positive pressure ventilation strategy. Recent work in ICU and general surgical patients has shown that LPV is only associated with favourable outcomes when the difference between Ppeak and PEEP (Driving Pressure: ΔP) is also decreased. Patients undergoing One Lung Ventilation (OLV) are at high risk of developing postoperative lung injury, therefore we investigated the association between intra-operative ΔP and outcome in this population.

With ethics approval we performed a retrospective casecontrol study of patients undergoing lung resection. Data was collated from a previous study examining critical care admission following lung resection. We used propensity matching to match 5 controls (not ventilated) to 1 case (ventilated for respiratory failure). Multivariate regression and best-subset model selection was used to determine the matched group. ΔP was recorded for duration of ventilation and a novel algorithm was created to detect the start and end of OLV, allowing exposure to ΔP during OLV to be calculated. These were modelled against the primary outcome of ventilation for respiratory failure. Length of hospital stay and worst recorded PaO₂:FiO₂ ratio 6-24 hours post-operatively were used as secondary outcomes. Exposure to Ppeak and tidal volume normalised to predicted body weight (TVpbw) were also assessed to allow for comparison to ΔP . Multivariate analysis was performed to adjust for potential confounders.

132 patients with complete ventilator data and the primary outcome of interest were included. Pre-operative % predicted diffusing capacity for carbon monoxide (%DLCO) and Thoracoscore (a risk model containing patient and surgical factors used in thoracic surgery) were applied as determinants of propensity of ventilation for respiratory failure. Initial univariate regressions did not demonstrate any association between ΔP , Ppeak, TVpbw and ventilation for respiratory failure (p>0.209 for all). This was also true for exposure to these variables during OLV (p>0.766 for all). Univariate regression for secondary outcomes showed no association with the three ventilator variables. Multivariate analysis did not result in any of the ventilator variables being associated with any outcome when adjusting for potential confounders.

Our study did not demonstrate any association between the ventilator variables and outcome following OLV. We hypothesise this is due to consistent use of LPV strategies in cardiothoracic anaesthesia, resulting in a homogenous study population with little variability in Ppeak, PEEP and TVpbw. Future work examining extremes of these variables may be required to show association with outcome.

Towards the immortalisation of primary human myoblasts derived from patients susceptible to malignant hyperthermia and their non-susceptible relatives

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Malignant hyperthermia (MH) is a pharmacogenetic condition whereby in susceptible individuals, a rapid hypermetabolic response results from skeletal muscle calcium dysregulation ¹. Current studies into MH are limited by the utility of nonhuman skeletal muscle models or human non-skeletal muscle cell lines such as HEK-293 cells ^{2,3}. Furthermore, experiments that use primary human tissue are inherently limited because of the rapid onset of replicative senescence that has been observed ⁴. Thus, there is a crucial need to develop methods that will extend the life of cells derived from patients who are susceptible to MH (MHS) and their non-susceptible relatives (MHN) in order to allow an improved understanding of the mechanisms that underlie the pathophysiology of the human MH reaction. This study aims to develop such human skeletal muscle cell lines derived from patients with unique mutations associated with MH as well as those from their MHN relatives.

Human biopsy samples taken for the diagnostic in vitro contracture tests were processed as previously described to isolate human myoblasts ⁵. Myoblasts from three MHS patients, three MHN family members and a non-related MHN individual, were infected using the γ -retroviral system to deliver genes encoding CDK-4 (cyclin dependent kinase) and hTERT (human telomerase reverse transcriptase). Successfully infected cells were selected using both puromycin (0.3 µg/ml) and hygromycin (50 µg/ml) for at least two weeks. Cells were then allowed to proliferate to over 10 doublings before undergoing fluorescent activated cell sorting (FACS) for CD56 and CD82 antigens in order to produce monoclonal and polyclonal pure myoblast cell lines.

Myoblasts from two MHS patients and four MHN patients survived dual antibiotic selection for at least two weeks. These cells proliferated from approximately 10 000 cells to over one million cells prior to undergoing FACS, following which they were clonally expanded. All immortalised samples were found to contain cells positive for both CD56 and CD82, a combination which has recently been reported to be a marker of myoblasts that are able to differentiate into myotubes ⁶.

The immortalisation of these six primary human samples from MHS and MHN patients is novel the best of our knowledge. The cells are currently undergoing further characterisation in order to produce a regenerative pool of cells that will have the ability to replicate by more than 100 doublings and potentially providing over 1×10^{30} cells per sample ⁴. This will yield sufficient human cells derived from MHS and MHN patients that can then be used for numerous detailed studies investigating the fundamental mechanisms involved in MH.

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Epidemiology of malignant hyperthermia in modern anaesthetic practice: the influence of different anaesthetic techniques on clinical presentation

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Malignant hyperthermia (MH) is a progressive hypermetabolic reaction that occurs in genetically susceptible patients in response to triggering anaesthetic agents: the inhalation anaesthetics and the depolarizing muscle relaxant, succinylcholine. Index cases may be referred for testing because they developed features suggestive of a hypermetabolic MH reaction: a severe hypermetabolic reaction can progress to muscle rigidity and rhabdomyolysis. Other index cases are referred because they developed exaggerated muscle rigidity following succinylcholine or unexplained postoperative rhabdomyolysis, both of which are more common in individuals who are susceptible to MH. Our main aim was to identify the effect of the use of different anaesthetic drugs on the development of variable clinical features of MH.

We included MH probands who were tested susceptible to MH using the *in vitro* contracture test (IVCT) between 1988 and 2017. Data were collected from copies of anaesthetic and perioperative records (where available), referral letters and copies of laboratory test results stored in the Leeds MH unit archive. We recorded the patient's age, sex, medical and anaesthetic history, details of drugs administered during anaesthesia, and the timing, nature and severity of clinical features associated with MH.

We collected data on 343 index cases, while 23 patients were excluded because of insufficient information. The mean age-at-episode of the included 320 patients was 24 years (range 2–74) and 66.9% (214 of 320) were males. In our cohort, 119 patients presented with both metabolic and muscular manifestations, 155 patients with hypermetabolic manifestations only and 46 patients presented with muscular rigidity. The reaction was triggered by both succinylcholine and inhalation agents in 171 patients, succinylcholine only in 53 patients and inhalation anaesthetics only in 96 patients.

Non-depolarising muscle relaxants (NDMR) were used in 95 patients and its use was associated with a statistically significant lower creatine kinase level, nevertheless, no significant effect of the use of NDMR on reducing the incidence of myoglobinuria or generalised muscular rigidity could be noticed. Four patients who received succinylcholine but no inhalational agent developed one or more features possibly suggesting a hypermetabolic MH reaction but alternative causes cannot be excluded because of a lack of information. The combination of succinylcholine and inhalation anaesthetics led to more severe MH reactions with both muscular and metabolic manifestations. The role of succinylcholine alone in triggering a hypermetabolic MH reaction remains controversial. NDMR reduce the severity of some manifestations of MH but does not protect against the development of a reaction in a susceptible patient.

Development of a Core Outcome Set for studies evaluating the effects of anaesthesia on perioperative morbidity and mortality within the hip fracture population

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Perioperative studies on hip fracture patients show a large degree of inconsistency in the outcomes they report and how these are defined. The objective was to develop a core outcome set for use in future perioperative hip fracture studies. This would improve the body of comparable evidence when evaluating interventions that affect patient care.¹

A systematic review of literature published between 2000 and 2015 identified all reported outcomes in perioperative hip fracture studies in the context of comparing one type of anaesthesia with another. From this, a list was compiled grouping similar outcomes together and removing duplicates. These outcomes were circulated within the first round of the Delphi questionnaire. Participants were asked to rate the importance of each outcome on a scale of 1 to 9 and suggest additional outcomes. A second round of Delphi provided feedback results and asked participants to rescore each outcome. This process was repeated in a third round of Delphi. Consensus that an outcome should be considered for inclusion at each stage was a score of 7 to 9 by 70% or more participants and a score of 1 to 3 by 30% or fewer participants. Participants represented seven major stakeholder groups globally including anaesthetists, orthopaedic surgeons, orthogeriatricians, nursing staff, physiotherapists, occupational therapists and patients. During two consensus webinars, each outcome and their inclusion in a final core outcome set was discussed at length.

The first round questionnaire contained 34 discrete outcomes obtained from a systematic review of the literature. Participants proposed an additional 98 outcomes during this round, the majority of which were similar and were re-categorised into four new outcomes. Thirty eight outcomes were entered for rounds 2 and 3. The number of participants completing rounds 1 to 3 were 242, 186 and 169 respectively. This represented a completion rate of 70%. Seventeen outcomes ranked critical by the Delphi panel were considered at two consensus webinars. Outcomes included from these were: mortality, time from injury to surgery, orthogeriatric input, delirium, acute coronary syndrome, acute kidney injury, hypotension, pain, out of bed at day 1, sepsis and pneumonia. They were categorised into domains representing true patient outcomes and processes of care deemed to be of importance.

We used robust consensus methodology to develop the first core outcome set for use in studies evaluating the effects of anaesthesia perioperatively in the hip fracture population. We recommend this set is used as a minimum number of outcomes reported in future studies in order to facilitate pooling of data and better comparisons between studies.²

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Contemporary perioperative management of ACE-inhibitors and angiotensin receptor blockers

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The control of perioperative blood pressure is a major clinical issue. Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are the commonest anti-hypertensive drugs used in higher risk surgical patients^{1,2}. Large database studies suggest continuing these medications perioperatively is associated with long-term morbidity³. Other observational studies however, offer conflicting conclusions⁴. To help the rationale behind the mechanistic, randomized controlled trial of Stopping Perioperative Angiotensin-II Converting Enzyme inhibitors/receptor blockers (SPACE;-ISRCTN17251494) we sought stakeholder opinion regarding the pre- and post-operative use of ACEi/ARBs.

We surveyed 29 key opinion leaders in perioperative medicine (POQI Consensus Conference 2016), 119 UK International Surgical Outcomes Study (ISOS) lead investigators, plus an open invitation to respond via the RCOA website. We asked what general prescribing patterns they believe are appropriate for ACEi/ARBs and presented clinical scenarios to examine whether these responses were internally consistent with their stated practice.

Of 194 responders, 96% practice in the UK and 84.5% are anaesthetic/ICU consultants. There is a marked divergence in perioperative practice as to whether either drug class should be continued/stopped (Fig. 7). Postoperatively, a systolic blood pressure of 90 mmHg in a stable patient would not deter 10% of clinicians from restarting the ACEi/ARBs if this represented their usual practice.

The preoperative scenarios revealed that if a patient was acutely hypertensive on the day of surgery, the decision to proceed had no correlation with clinician preference to stopping or continuing ACEi/ARBs (Odds Ratio: 1.19 (95% confidence interval:0.60–2.37)). Faced with acute hypertension and myocardial injury within 24 hours after surgery, only 57% of clinicians, who would routinely restart normal ACEi/ARB therapy with 24 hours, would use these drugs in this scenario (Odds Ratio: 0.86 (95% confidence interval 0.43–1.69)).

This survey provides support that a mechanistic trial such as SPACE is essential. Seeing such a variation in clinical practice with regards to pre- and post-operative management of ACEi and ARBs highlights the need for clear evidence based guidelines.



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Reduction in hospital length of stay via tracheostomy quality improvement collaborative

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The Global Tracheostomy Collaborative (GTC) is a quality improvement collaborative, aimed at improving health outcomes for tracheostomy patients globally. Improving Tracheostomy Care (ITC) program introduces the GTC resources into twenty diverse UK NHS Hospitals. Sixty global sites enter patient-level data into the GTC database, collecting demographic and comorbidity data, along with surrogate indicators for the quality and safety of care. Surrogates include use of augmented communication methods and speaking valve use, which may impact on decannulation rates and length of stay.^{1,2,3} The aim of this project was to analyse early data collected from UK ITC sites and compare key metrics with global GTC sites.

Pooled data were extracted from the ITC and GTC REDCapTM databases and simple comparisons made using Microsoft ExcelTM. Fishers exact test was used for analysis of 2×2 contingency tables and Mann Whitney U test used for exploring differences between groups for non-parametric data.

Data were analysed for 225 ITC tracheostomy admissions and 2634 GTC admissions. Comparisons are shown in Table 4, with total records available for comparison per category listed (not all patients had all data fields completed). The ITC sites were significantly better at attempting augmented communication methods than GTC sites, although GTC sites used more speaking valves with ventilation. Decannulation rates and hospital length of stay was significantly lower in the ITC sites. Mortality was not significantly different between these cohorts.

	GTC (global)		ITC (UK)		Fishers exact p
	%	Total records	%	Total records	
Attempts at augmented communication	23.1	551	42.6	54	<0.01
Speaking valve use	35.8	589	37.2	94	0.82
Speaking valve use with ventilation	6.6	210	0.0	94	<0.01
Mortality	13.1	2355	16.0	144	0.31
Decannulation	27.6	2349	41.7	156	<0.01
	Median	IQR	Median	IQR	Mann Whitney U p
Total hospital length of stay (days)	34	47	26	40	0.03

Early data from this group of NHS Hospitals suggests that UK tracheostomy patients have a greater focus on communication, perhaps reflecting better multidisciplinary and speech & language therapy integration than international sites.^{2,3} Better communication can lead to greater patient motivation and involvement in their care, perhaps contributing to higher decannulation rates and reduced length of stay.^{1,3} Further exploration of the different contextual factors present in the ITC and GTC hospitals is warranted.

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Effectiveness of Above Cuff Vocalisation for ventilator-dependent patients with tracheostomies

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Cuffed tracheostomy tubes facilitate invasive ventilation in patients admitted to Intensive Care Units (ICUs). Inflated cuffs prevent laryngeal airflow and vocalisation. Sub-glottic suction tubes such as the 'Blue Line Ultra SuctionaidTM' (BLUS) are used primarily to remove sub-glottic secretions, but retrograde gas flows via the suction port can facilitate Above Cuff Vocalisation (ACV).^{1,2,3} The aims of this study were to assess whether patients could achieve an audible voice using ACV and to assess potential benefits of ACV for communication.

The study (Reference 15/NW/0464, IRAS 178997) recruited unselected, ventilator-dependent, adult ICU patients who had a cuff-inflated BLUS tube in situ for ventilatory support. Consenting participants underwent Fibreoptic Endoscopic Assessment of Swallow (FEES) by experienced Speech & Language Therapy staff with and without ACV. Clinical assessment of voice quality were recorded using Therapy Outcome Measure for Voice Impairment (TOMS), GRBAS and the ICU Functional Communication Scale (FCS). Median differences between paired observations were analysed with SPSS 23 (IBM Corp) using Wilcoxon signed-rank test for these ordered categorical scales. The primary outcome was to assess whether patients could achieve an audible voice using ACV.

Ten patients completed the study, using ACV for medians of 3 days, 9 episodes and 15-minute durations. ACV resulted in an audible voice (speech or whisper) in 8 of the 10 patients, during 66 out of 91 ACV attempts (72.5%). Voice quality assessment using the GRBAS scale (each domain scored from 0-normal to 3-high degree) demonstrated median (IQR) scores for ACV voice were as follows: GRBAS Grade 3(1), Roughness 2(1), Breathiness 2(3), Asthenia 2(2) and Strain 2(3). Eight out of ten patients had significantly improved TOMS voice scores (p=0.01) and six out of ten had significantly improved FCS scores (p=0.02). ACV effectiveness shown in Table 5.

	Count	%
No voice	25	27.5%
Whisper	29	31.9%
Speech	37	40.7%
Speech or Whisper	66	72.5%
Total ACV episodes	91	100.0%

ACV can achieve effective vocalisation in ventilatordependant ICU patients. ACV has the potential to aid earlier, more effective communication and is an important option to add to the range of communication tools available to the ventilator-dependent patient.

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Changes in tracheostomy tube positioning with patient repositioning: the Lunar positioning study

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Suboptimal placement of tracheostomy tubes is difficult to detect and may contribute to device displacement, especially if associated with patient repositioning. Previous evaluation of endoscopic views to assess tube position described the tracheoscopic (T-view) or trans-laryngeal (L-view) along with scoring systems to describe the position of the tube. The aim of this secondary analysis of the original data was to investigate discrepancies between positioning scores from a hyperextended neck position to facilitate new tracheostomy insertion to a 30-60 degree head-up position for continuing nursing care.

Adult ICU patients requiring new tracheostomies were recruited (NCT01356719). At new tracheostomy insertion, paired T and L-views were taken in the hyper-extended 'insertion' position and the head-up 'nursing' position. Images were later scored by five independent raters using bespoke scoring systems, previously described.¹ Comparison between positions with ordinal scoring systems used Wilcoxon Signed Rank Test and continuous scores used paired sample T tests. The primary outcome was to determine significant differences in tube position when the patient was moved following new tracheostomy insertion.

Fourteen patients had paired images taken in the two positions, making 70 comparisons (five raters) with each of eight scoring systems. Table 6 demonstrates five out of nine scoring systems generated significant differences between pre and post scores, with five scoring systems producing a one or more category difference with over 50% of comparisons. Through a unique consensus and prioritisation exercise using front line staff and leaders from twenty participating UK hospitals, we aimed to develop a national strategy for prioritisation of tracheostomy QI strategies.

Scoring system	Different scores pre/post		Median scores		Wilcoxon p
	N (total = 70)	%	Insertion (pre)	Nursing (post)	
L3	29	41.4	3	3	0.15
L5	39	55.7	4	4	0.57
Т%	26	37.1	75	75	0.045
T Quad	27	38.6	3	3	0.46
T Quad Grid	20	28.6	3	3	0.02
			Mean scores		Paired T p
L VAS	66	94.3	75	68	0.04
T% eyeball	53	75.7	72	64	0.02
T Grid %	57	81.4	70	64	0.04
T VAS	55	78.6	72	67	0.07

Table 6 Comparisons between different positions.

Whilst the merits of the different scoring systems require further evaluation, what this study does demonstrate is that changing the patient's position following tracheostomy insertion leads to a difference in the majority of scoring systems used. This likely represents genuine change in the tube position relative to the trachea. The clinical significance of this is unknown, but endoscopic evaluation of the tube in both hyper-extended and sitting positions would seem a sensible precaution following tracheostomy.

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Collaborative national consensus and prioritisation of tracheostomy quality improvements in the United Kingdom

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Tracheostomies are artificial airway devices and whilst a potentially lifesaving procedure, tracheostomy can also lead to significant morbidity and mortality¹. Associated problems with vocalization and swallowing can lead to anxiety for patients, families and healthcare staff. The Global Tracheostomy (Quality Improvement, QI) Collaborative supports participating sites with a variety of strategies and resources which have been shown to improve the quality and safety of care in participating institutions, leading to a large-scale UK-wide evaluation. However, whilst individual strategies have proved effective in single centres, it is unclear which QI program elements should be prioritised in the diverse hospitals of the UK's National Health Service.^{2,3}

The study received a favourable opinion from the national research ethics committee (IRAS ID 206955). Multidisciplinary staff groups were interviewed and completed bespoke Appreciative Inquiry (AI) questionnaires regarding their experiences of tracheostomy care and associated attempts at QI. Qualitative evaluation of transcripts developed key themes. These were further refined at a multidisciplinary meeting of site leads by group consensus, constructing 22 'Dotmocracy' idea rating sheets, each containing a statement around tracheostomy improvement strategies. Participants each ranked the statements by placing sticky dots onto the sheets. These were later scored using a weighted 5-point Likert scale, bounded by strong agreement, through neutral to strong disagreement.

Transcripts from 39 staff interviews produced 16 statements, with a further 6 statements developed from AI and focus groups. Forty-eight participants prioritised these statements during the 'Dotmocracy' voting. Highly ranked priority interventions included multidisciplinary staff education, developing standards and competencies, implementing multidisciplinary ward rounds, ensuring equipment standardisation and providing structured care bundles.

Our qualitative process and 'Dotmocracy' voting has allowed us to build a national 'to-do' list of relevant tracheostomy QI interventions. Understanding the priorities that front-line staff have in implementing distinct QI interventions will allow focus on those elements that are considered important and necessary, likely resulting in more effective implementation.

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