

ABSTRACTS FROM THE ANNUAL MEETING OF THE SURGICAL RESEARCH SOCIETY OF AUSTRALASIA, 2009

Mycoplasma fermentans in acute Crohn's Disease. A preliminary report of a putative aetio-pathogenic agent

William E. Roediger, Adrian Cummins, Jennifer Burke and Ross Philpot

Background and aims:

Infective organisms have gained credibility in the causation of Crohn's disease. Potential infective agents need to explain oral ulceration, eye changes, perianal ulceration, joint changes and enteric ulceration. With the exception of enteric ulceration all are associated with *Mycoplasma* invasion. The aim of this study was to detect *Mycoplasma* in the entero-epithelium of acute and chronic Crohn's disease.

Methods:

Tissue from Crohn's cases (8) and disease control (7) were subjected to the following: DNA staining, PCR and amplicon analysis for *Mycoplasma fermentans*, *Mycoplasma fermentans* lipopeptide antibody staining and notation of therapeutic responses in those cases that accepted macrolide antibiotic treatment.

Results:

Two cases of chronic fistulizing Crohn's disease showed multiple foci of intracytoplasmic DNA staining in crypt epithelium but not in laminal immune cells. PCR analysis of 3 cases of acute Crohn's disease were positive for *Mycoplasma fermentans* confirmed by amplicon DNA comparison with reference sequences. Three cases of chronic stricturing Crohn's disease were negative for *Mycoplasma fermentans* on PCR but all showed positive *Mycoplasma fermentans* lipopeptide antibody staining of immune cells scattered between layers of fibrous tissue. Two cases of acute Crohn's disease accepted four weeks treatment of Clarithromycin with histological and radiological clearance of mucosal ulceration.

Conclusion:

DNA analysis in acute Crohn's disease suggests mycoplasmal involvement in acute Crohn's disease. Antibiotic treatment responses do not favour opportunistic infection. Chronic Crohn's disease may be antigenically driven by mycoplasmal lipopeptide which remains detectable in the absence of mycoplasmal DNA. Our preliminary positive results of *Mycoplasma fermentans* should encourage a wider study of *Mycoplasma fermentans* in acute Crohn's disease.

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Burn injury alters distant nerve density in animal and human model

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Introduction:

Cutaneous innervation is critical to normal skin function. One of the most common disruptions to cutaneous innervation is injury causing damage or ablation of cutaneous nerves. Repair of cutaneous innervation post burn injury is poorly understood, but sustained sensory abnormalities in scar tissue are commonly reported, suggesting functional return is limited.

Methods:

We have investigated the consequences of cutaneous burn injury on innervation at both the site of injury and non-injured sites in both a rat and human model.

Results:

Analysis of neuroanatomy in a rat model at 12 weeks post-injury shows significant decreases in the extent of innervation at both injured and non-injured sites. Similarly, analysis of human patients with unilateral burn injuries shows the extent of innervation in both injured and non-injured sites is strongly correlated, with decreasing innervation at both sites as the extent of injury increases. However, whilst sensory function is diminished in the scar sites, no apparent loss of sensory function was observed in the non-injured sites.

Conclusions:

Together, this data provides strong evidence for a systemic response to burn injury that decreases the extent of cutaneous innervation. However, this systemic change does not appear to negatively impact on sensory function. The mechanism and impact of these systemic changes will be important to understand as wound healing research continues to strive for regeneration rather than repair.

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Meta-Analysis Of Laparoscopic Posterior And Anterior Fundoplication For Gastro-Oesophageal Reflux Disease

Siddaiah-Subramanya M¹, Belal M³, Khan S³, Memon B², Memon M A^{2, 4, 5}

Introduction:

Although laparoscopic posterior (Nissen) fundoplication (LPF) provides good control against the gastro-oesophageal reflux, there remain problems with the postoperative dysphagia and the inability to belch or vomit. To decrease these postoperative complications of LPF, laparoscopic anterior fundoplication (LAF) was introduced. The aim was to conduct a meta-analysis of RCTs to investigate the merits of LPF vs LAF for the treatment of gastro-oesophageal reflux disease (GORD).

Method:

A search of Medline, Embase, Science Citation Index, Current Contents, PubMed and Cochrane Database identified all RCTs comparing different types of laparoscopic posterior and anterior fundoplications published in the English Language between 1990 and 2008. The eight variables analysed included operative time, overall complications, conversion rate, re-do operative rate, dysphagia score, heartburn rate, visick grading of satisfaction and overall satisfaction.

Results:

Five trials totalling 556 patients (Posterior=277, Anterior=279) were analysed. The analysis showed trends favouring LPF in terms of overall complication rate, conversion rate, incidence of postoperative heartburn and re-do operative rate. There was a significant improvement in the overall satisfaction score among patients favouring LPF while, there was a significant reduction in dysphagia score favouring LAF. No difference was noted in operating time and Visick's grading of satisfaction between the two groups.

Conclusion:

Based on this meta-analysis, LPF is associated with fewer complications, decreased rate of conversion, heartburn and re-operation, and significantly higher overall satisfaction among patients. However the LAF was associated with significantly lower incidence of dysphagia. We therefore conclude that LPF is a better alternative to AFP at the expense of higher dysphagia rate.

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Association of statin prescription with small abdominal aortic aneurysm progression

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Introduction:

Statins have been suggested to reduce expansion of abdominal aortic aneurysms (AAA) independent of lipid lowering effects.

Methods:

We assessed the association of statin treatment and serum low density lipoprotein (LDL) concentrations with small AAA expansion. 652 patients undergoing surveillance of small AAAs were entered into the study from five vascular centres. In a subset fasting lipids (n=451) and other biomarkers (n=216) were measured. AAA diameter was followed by ultrasound surveillance for a median of 5 years.

Results:

349 (54%) of the patients were prescribed statins. Adjusting for other risk factors statin prescription was not associated with AAA growth (odds ratio, OR, 1.23, 95% confidence interval, CI, 0.86-1.76). Above median AAA growth was positively associated with initial diameter (OR 1.78 per 4.35mm increase in diameter, 95% CI 1.49-2.14) and negatively associated with diabetes (OR 0.37, 95% CI 0.22-0.62). Above median serum LDL concentration was not associated with AAA growth. Patients receiving statins had lower serum C-reactive protein concentrations but similar matrix metalloproteinase-9 and interleukin-6 concentrations to those not prescribed these medications.

Conclusions:

We found no association between statin prescription or LDL concentration with AAA expansion. The results do not support the findings of smaller studies and suggest that statins may have no benefit in reducing AAA progression

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Sportsman's Hernia – An Australian Problem

John Garvey, John Read

Introduction:

The name **sports hernia** was coined by Adelaide Sports Physician Greg Lovell to describe an injury prevalent in kicking sports such as Australian Rules Football. The presenting symptoms are groin pain, discomfort, ache or lower abdominal pain but without a visible or palpable hernia being present. That is, the hernia is occult or hidden but can be a career-limiting injury for Australian Rules Footballers. In any first-grade team, two or three players will be carrying such an injury.

The injury was recognised as an Australian problem because it was initially described in Australia Rules Football players. It has been variously known as athletic pubalgia in 1970s and 1980s literature, hockey groin syndrome, posterior inguinal canal deficiency, osteitis pubis, baseball pitcher/hockey goalie syndrome, etc. The condition had been reported in Italian soccer players in the 1930s and in the UK amongst elite soccer players it is known as Gilmore's Groin.

Methods:

The clinical examination usually will not detect a hernia so diagnostic imaging has to be undertaken which shows a bulge through the posterior wall of the inguinal canal evident on straining. Accurate diagnosis of the injury came with the development of diagnostic ultrasound and MRI scanning when sports hernia was initially called "incipient direct inguinal hernia".

Results:

A unique operation is performed which is known as **a groin reconstruction operation** which has rejuvenated the careers of many elite footballers in several codes.

Conclusion:

Sports hernia is difficult to diagnose clinically but once documented, has a 95% success rate after surgical reconstruction. Because of the unique nature of Australian Rules Football, this condition has been documented and treatment has beneficial implications for groin injury sufferers in other sports and in other countries. Clinical research on this condition has also gained wider benefits to the community in general, particularly injured workers.

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Does Remote Ischemic Preconditioning Prevent Delayed Hippocampal Neuronal Death following Transient Global Cerebral Ischemia in Rats?

Saxena Pankaj, Bala Arul, Campbell Kym, Meloni Bruno, d'Udekem Yves and Konstantinov Igor E.

Introduction:

To determine if remote ischemic preconditioning (RIPC) induced by transient limb ischemia is protective against delayed hippocampal neuronal death in rats undergoing transient global cerebral ischemia (GCI).

Methods:

To determine if remote ischemic preconditioning (RIPC) induced by transient limb ischemia is protective against delayed hippocampal neuronal death in rats undergoing transient global cerebral ischemia (GCI).

Results:

There was no significant difference between the RIPC group and the ischemia only group. The number of neurons in the RIPC group were 0.90 (95% CI 0.20, 4.08) times the number in the ischemia group ($p=0.89$). The number of neurons in the RIPC group were 0.03 (95% CI 0.01, 0.10) times the number in the Control group ($p=0.0001$).

Conclusions:

Second window of the RIPC does not prevent hippocampal CA1 neuronal death at 7 days after transient global cerebral ischemia.

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Haemangioma: A Developmental Anomaly of Aberrant Proliferation and Differentiation of Neural Crest Cells Governed by the Renin-Angiotensin System

Itinteang T^{1,2}, Day DJ^{1,2}, Tan ST¹⁻³

Introduction:

Haemangioma, the most common tumour of infancy, affects about 10% of infants. The observation of the segmental distribution of a subgroup of haemangioma associated with midline structural abnormalities (PHACES syndrome) have led us to hypothesise a role for neural crest cells in the aetiology of haemangioma.

The serendipitous observation in 2008 of accelerated involution of haemangioma following Propranolol treatment led us to investigate the role of, the renin-angiotensin system (RAS) in accelerating haemangioma involution. We propose that the RAS modulates neural crest cell derived stem cell proliferation/differentiation and accounts for the natural progression of haemangioma.

Methods:

Immunohistochemistry was performed on paraffin sections from proliferating haemangioma lesions, and stained for endothelial (CD31), haemopoietic (CD34), mesenchymal (CD29), stem cell (CD133), neural crest cell markers (p75, nestin & vimentin), angiotensin converting enzyme (ACE), and angiotensin II receptors 1 & 2 (ATIIR1 & ATIIR2). The ability of angiotensin II (ATII) to induce proliferation in cells isolated from proliferating haemangioma biopsies was also investigated.

Results:

The cells lining the immature capillaries of proliferating haemangiomas are immuno-reactive for endothelial (CD31), haemopoietic (CD34), mesenchymal (CD29), stem cell (CD133), neural crest cell markers (p75, vimentin and nestin) and for ACE and ATIIR2.

Proliferation assays demonstrate that ATII increases cell proliferation in cultures prepared from proliferating haemangioma biopsies.

Conclusion:

Our results show a role for neural crest cells in the aetiology for haemangioma. The expression of ACE and ATIIR2 within proliferating lesions, and the high levels of circulating renin in infants support a role for the RAS in driving the proliferation seen in haemangioma. We propose that Propranolol decreases renin activity, which decreases conversion of angiotensinogen to angiotensin I, resulting in decreased ATII in haemangioma tissue leading to involution.

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Oesophago-gastric junction pressure characteristics differ for water and bread swallows in fundoplication patients with post operative symptoms

Myers JC, Jamieson GG, Thompson SK, Devitt PG.

Introduction:

After fundoplication, solids cause dysphagia more commonly than liquids but standard manometry evaluates oesophageal responses to liquid (water). This study evaluates oesophageal manometric features of bread swallows after fundoplication.

Methods:

Patients referred for evaluation of post operative symptoms (reflux or dysphagia) following a fundoplication underwent oesophageal manometry with 10 x 5mL water; and 4 bite-size bread swallows. Visual analogue scales were used to assess heartburn and dysphagia.

Results:

67 subjects were referred. Patients with large hiatus hernia, atypical symptoms or a mixture of symptoms were excluded, resulting in 2 groups: 22 patients with reflux and 13 patients with dysphagia. Oesophageal peristalsis for water swallows was similar for the two groups ($p=0.79$). Pressures at the oesophago-gastric junction (OGJ) in the 2 groups showed:

WATER swallows (Pressure mmHg)	OGJ pressure *	Ramp pressure *	Relaxation pressure *	Dysphagia score Liquids 0-10*
Reflux Patients	9.5 (6-22)	10 (8-15)	3.5 (1-8)	3.6 (0-8)
Dysphagia Patients	23 (22-32)	26 (21-29)	12 (7-19)	7.2 (4-10)
BREAD swallows (Pressure mmHg)	% Primary Peristalsis	Ramp pressure*	Relaxation pressure*	Dysphagia score Solids 0-10*
Reflux Patients	75 (50-100)	14 (9-23)	4 (2-7)	0 (0-3)
Dysphagia Patients	75 (50-88)	36 (35-37)	23 (14-29)	5 (5-6)

(data are median (IQR), Mann-Whitney U statistic * $p < 0.002$ Reflux vs Dysphagia patients)

Distal ramp pressure, OGJ resting & residual relaxation pressure and dysphagia scores were significantly higher in dysphagia patients compared to reflux patients for both water and bread swallows. Manometric features were greater for bread swallows in dysphagia patients.

Conclusions:

Bread swallows accentuate oesophago-gastric junction manometric features in post fundoplication patients with troublesome dysphagia.

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The humoral response after laparoscopic versus open colorectal surgery – a meta-analysis.

Sammour T, Kahokehr A, Chan S, Booth RJ, Hill AG

Background:

The local and systemic humoral response after colorectal surgery is thought to affect post-operative recovery. Despite a large number of trials comparing this response between laparoscopic and open surgery, results are conflicting. We aimed to systematically review the results from randomised controlled clinical trials comparing the humoral response after laparoscopic versus open colorectal surgery.

Methods:

A high-sensitivity search was conducted independently by two of the authors with no language restriction. Studies were identified from the Cochrane Central Register of Controlled Trials (CENTRAL/CCTR), Cochrane Library, Medline (January 1966 to January 2009), PubMed (1950 to January 2009) and Embase (1947 to January 2009). Relevant meeting abstracts and reference lists were manually searched. Data analysis was performed using Review Manager Version 5.0.

Results:

Thirteen randomised controlled trials were included. Meta-analysis demonstrated a significantly higher serum IL-6 on day 1 after open colorectal resection for neoplasia (n = 97) compared with laparoscopic resection (n = 76, p = 0.0008) without significant heterogeneity. Data for plasma IL-6 were heterogeneous, with no apparent difference between groups. No other significant differences were identified, and there were not enough data on local peritoneal humoral factors to allow meta-analysis.

Conclusion:

Open colorectal resection for neoplasia is associated with higher post-operative serum levels of IL-6 on day 1 than equivalent laparoscopic surgery. The aetiology and clinical significance of this finding is uncertain, and further studies are required to elucidate any differences in the local humoral response which may be more clinically relevant in surgery for this indication.

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Hospital Caseload and Outcome in Major Upper Gastrointestinal Surgery

Govind Krishna, John McCall

Introduction:

Internationally there is evidence of improved outcomes when major surgical procedures are performed in high volume hospitals, but this relationship has not been examined in the New Zealand setting.

Objective:

To compare peri-operative (day stay, morbidity and mortality) and long term outcome after major upper gastrointestinal surgery (oesophago-gastrectomy = OG, total gastrectomy = TG, pancreatico-duodenectomy = PD) performed in a tertiary (high volume centre = HV) and three provincial (low volume centre = LV) hospitals in New Zealand .

Methods:

All OG, TG, and PD performed between January 1997 and December 2006 in the four hospitals were identified from audit data, manual search of operation registers, hospital discharge codes, and data held by New Zealand Health Information Services. Demographic, diagnostic, disease-stage, co-morbidity, day stay, morbidity and mortality data were collected. Standard classification systems were used to grade co-morbidities (Charlson score) and complications (Clavien score). Baseline characteristics and outcomes were compared between the HV and three LV hospitals (chi-square, unpaired t-test, odds ratios) and adjusted for major variables (logistic regression).

Results:

346 patients underwent surgery (OG 133, TG 94, PD 119) at the HV (219) and LV (127) hospitals. Baseline characteristics including Charlson and ASA score were similar, although more HV patients had benign disease (22% v 6%; $p=0.0005$). Mean hospital stay was 19 days for HV and LV, and readmission to ICU was similar (OR 0.6, 95%CI 0.3-1.2). Post-operative morbidity scores were significantly higher in the LV hospitals ($X^2 =14.6$; $p=0.006$), particularly for OG, but post-operative mortality was not different (7.7% vs 7.8%). Late mortality was not different, although cause of death data was not available. These results persisted after adjusting for major variables.

Conclusion:

Patient populations undergoing major upper GI surgery were similar except malignant diagnosis was more common in LV patients. The HV hospital had a lower rate of post-operative complications but other outcome measures including mortality were similar.

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A prospective case-control study of the local and systemic cytokine response after laparoscopic versus open colonic surgery.

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Background:

There is a sequential, high concentration cytokine response after major abdominal surgery. The magnitude of this response has been directly linked to post-operative metabolic derangement, ileus, adhesions, and oncological outcomes. We aimed to compare the local and systemic cytokine response in laparoscopic and open colonic surgery and relate this to post-operative recovery parameters.

Methods:

Using a prospectively collected patient database, we compared a Study Group (n = 50) of patients undergoing elective laparoscopic colonic resection with a Control Group (n = 25) of patients undergoing equivalent open colonic surgery within an ERAS program. Patients were matched for age, sex, BMI, ASA, Cr Possum, side of resection, diagnosis, and histological stage. Plasma and peritoneal fluid concentrations of IL-6, IL-8, IL-10, and TNF α were measured at 20 – 24 hours after surgery. The Surgical Recovery Score was determined pre-operatively and at 3, 7, 30, and 60 days post-operatively. All data were prospectively collected, and *a priori* definitions were used for discharge parameters, complications, and complication severity.

Results:

Peritoneal fluid IL-6 concentration was lower after laparoscopic surgery. There were no significant differences in the other cytokines measured, or in any post-operative recovery outcomes. Significant correlations were found between cytokine levels and discharge criteria achievement, day stay, post-operative complications, and the Surgical Recovery Score.

Conclusion:

With the exception of a lower peritoneal IL-6 level, the systemic and peritoneal cytokine response at 20-24 hours is similar after laparoscopic versus open colonic resection within an ERAS program, with corresponding equivalent rates of post-operative recovery.

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Remote Ischemic Preconditioning Stimulus Decreases Expression of Kinin Receptors in Human Neutrophils.

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Introduction:

Kinins are involved in remote ischemic preconditioning (RIPC) by acting via G protein-coupled receptors (GPCR) - B1 and B2 receptors. Interaction of the kinins with GPCR receptors possibly results in internalization of the receptors within signalosome to transfer the signal to mitochondria. We hypothesized that RIPC significantly decreases the expression of kinin receptors on the surface of neutrophils.

Methods:

The study was performed on 5 healthy male volunteers. Left forearm was rendered ischemic for three 5-min periods, each separated by 5 min of reperfusion. Three venous blood samples were taken from the right arm - one before and two after the RIPC stimulus. Neutrophil isolation, immunofluorescence labelling and confocal microscopy were performed. Mean pixel intensity data was generated using a fixed circular area of interest (AOI, 40x40 μm). For every image, the AOI was placed over a cell and the mean pixel intensity was recorded. The mean intensity was expressed as pixel $\times 10^2/\mu\text{m}^2$ and presented as mean \pm SEM. Immunofluorescence at the different time points was compared by one way analysis of variance with Bonferroni's post-hoc test. A p-value <0.05 was considered significant.

Results:

The mean pixel intensity for B1 receptors was decreased at 24 hrs after RIPC when compared with both baseline and 15 min after RIPC ($p < 0.001$). Similarly the intensity for B2 receptors was decreased at 24 hrs after RIPC when compared to the baseline value ($p < 0.001$).

Conclusions:

Decreased expression of kinin receptors after RIPC stimulus is consistent with signalosome theory.

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Suspected Venous Thromboembolism: the Epidemiology, Clinical Characteristics and Treatment of Patients Presenting to the Emergency Department

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Introduction:

To evaluate the clinical characteristics of patients, treatment modalities used and assess the incidence of venous thromboembolism (VTE) in patients presenting to the emergency department (ED).

Methods:

A prospective observational study was undertaken on 1308 patients presenting to the ED in 2008 with symptoms of lower extremity swelling and/or pain, redness suggestive of deep vein thrombosis (DVT) or symptoms/signs suggestive of acute pulmonary embolism (PE) i.e. shortness of breath, chest pain, haemoptysis. VTE risk, prior hospitalization, source of referral, type and duration of prophylaxis and VTE rate were assessed.

Results:

Median age was 42 years (27.5–54.5). Male to female ratio was 1:2. 78% of patients were admitted during ED working hours and 19.5% out of hours. The local medical officer referred 39.1% of patients whereas 60.9% were self-- - referrals from the community by self-- - presentation or by ambulance. 23.2 % of patients had a prior history of VTE. 23.2% of patients had a prior hospital admission in the last 3 months. Duplex ultrasonography and D-- - dimer was performed in 62.3% and 30% of patients respectively. 14.5% of patients had a ventilation perfusion lung scan whereas 40.6% of patients had CT pulmonary angiogram. Our VTE incidence was 69.6% (95% CI: 57.9%-- - 79.2%). 39.1% of patients had a non-- - fatal PE. 16% of patients had a proximal DVT whereas 13% had distal DVT. 47.8% of patients required a ward admission. 72.9% of patients were treated with both enoxaparin and warfarin, 18.8% with enoxaparin only, and 8.3% with warfarin only. There was no major bleeding complications.

Conclusion:

Given the high incidence of DVT, non fatal and fatal PE our results reinforce the need for accurate identification of hospitalized patients at risk of VTE and the use of prophylactic modalities. It also emphasizes the need of extended prophylaxis beyond hospitalization in certain high risk groups. These results will assist to refine and redefine recommendations in the diagnosis and management of VTE in the aED.

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Warming and humidification of insufflation gas in laparoscopic colonic surgery – a double-blinded, randomised, controlled trial.

Sammour T, Kahokehr A, Hayes J, Hulme-Moir M, Hill AG

Background:

Warming and humidification of insufflation gas is thought to be beneficial in laparoscopic surgery, but evidence in prolonged laparoscopic procedures is lacking. We aimed to test the hypothesis that warming and humidification of insufflation CO₂ would lead to reduced post-operative pain and improved recovery by reducing peritoneal inflammation in laparoscopic colonic surgery.

Methods:

Multicenter, double-blinded, randomised controlled design. The Study Group received warmed (37°C), humidified (98%RH) insufflation carbon dioxide, and the Control Group received standard gas (19°C, 0%RH). Anaesthesia and analgesia regimens were standardised. Intra-operative core temperature was measured at 15min intervals using an oesophageal probe. At the conclusion of surgery the primary surgeon was asked to rate camera fogging on a Likert scale. Post-operative opiate usage was determined using Morphine Equivalent Daily Dose (MEDD), and pain was measured using visual analogue scores. Peritoneal and plasma cytokine concentrations were measured at 20h post-operatively. Post-operative recovery was measured using defined discharge and complication criteria, and the Surgical Recovery Score.

Results:

Eighty two patients were randomised, with 41 in each arm. Groups were well matched at baseline. Intra-operative core temperature was similar in both groups. Median camera fogging score was significantly worse in the Study Group (4 vs. 2, $P = 0.040$). There were marginal differences in pain scores, but no significant differences were detected in MEDD usage, cytokine concentrations or any recovery parameters measured.

Conclusion:

Warming and humidification of insufflation CO₂ does not attenuate the early inflammatory cytokine response, and confers no clinically significant benefit in laparoscopic colonic surgery.

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Chitosan nanoparticles enhance Dz13 efficacy against osteosarcoma

Tan, ML, Dunstan DE, Broadhead ML, Friedhuber AM, Choong PFM, Dass CR

Introduction:

Dz13 is a DNA enzyme that cleaves c-Jun mRNA, and is capable of inhibiting cancer cell growth in vitro. Efficacy in vivo depends on use of a suitable drug delivery system (DDS). Chitosan is a biomaterial that is abundant in nature, inexpensive, safe, biocompatible and biodegradable. We tested chitosan for the delivery of Dz13.

Methods:

Dz13 can be encapsulated into chitosan nanoparticles¹, though this formulation needed optimisation. For optimisation of this chitosan-based formulation, formulation buffer pH, chitosan concentration and temperature were variables tested. Particles were characterised biophysically with electron microscopy, dynamic light scattering, and surface charge determination. The potencies of the various Dz13-nanoparticles were gauged in vitro with trypan blue and the TUNEL assay. Particles were tested in two different clinically-relevant disease models, and using a clinically-adoptable dosing regimen. Free Dz13 was also administered intravenously into mice bearing orthotopic tumours for comparison.

Results:

Particles were 50-300 nm in diameter and encapsulated Dz13 was active when particles were exposed to cancer cells. Nanoparticles were stable during storage for a month, but were not stable in mouse and human sera. Dz13-nanoparticles were shown to be efficacious against osteosarcoma. No toxicity was observed with the formulation, and no side-effects were noted in lymphatic and reticuloendothelial tissues proximal and distal to the administration site. Non-encapsulated Dz13 did not show efficacy.

Conclusions:

The chitosan nanoparticulate formulation enhanced Dz13 activity in vitro, and efficacy in vivo. Particles were also biocompatible in vivo. This DDS may have some beneficial effect if tested clinically with Dz13. ¹

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¹ Dass, C.R., Friedhuber, A.M., Khachigian, L.M., Dunstan, D.E., and Choong, P.F.M. Biocompatible chitosan-DNAzyme nanoparticle exhibits enhanced biological activity. J Microencaps 2008;25:421-425.

Decoding the anti-osteosarcoma properties of Pigment Epithelium-Derived Factor (PEDF)

Broadhead ML, Choong PFM, Dass CR

Introduction:

Pigment Epithelium-Derived Factor (PEDF) is an endogenous glycoprotein with direct and indirect activity against osteosarcoma. As a potent anti-angiogenic it specifically targets tumour vasculature whilst also inhibiting osteosarcoma progression². Little is known of the molecular mechanisms employed by PEDF to achieve this. The purpose of this study is to provide a mechanistic understanding of PEDF activity. This forms the foundation for identifying key molecular mediators and pathways for PEDF.

Methods:

Two osteosarcoma cell lines, SaOS-2 and SJSA-1, were treated with 200nM and 100nM PEDF respectively. Cell proliferation assay was performed by 4',6-diamidino-2-phenylindole (DAPI) stain. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) and Ki67 staining was then used to evaluate the role of apoptosis and cell-cycle control. Scanning electron microscopy sought ultrastructural evidence of PEDF activity against SaOS-2.

Results:

SaOS-2 treated with 200nM PEDF and SJSA-1 treated with 100nM PEDF demonstrated a 62% ($p < 0.05$) and 63% ($p < 0.05$) reduction in cell number respectively by DAPI stain. There were 59% ($p < 0.05$) and 75% ($p < 0.01$) increases in TUNEL positive staining SaOS-2 and SJSA-1 cells, while PEDF treatment was also associated with 47% ($p < 0.001$) and 55% ($p = 0.06$) reductions in strongly positive Ki67 staining cells. Ultrastructural features associated with PEDF treatment included chromatin condensation, disorganisation of mitochondria and prominent cell surface processes.

Conclusions:

The induction of apoptosis and cell cycle control appear to be critical processes employed by PEDF for its anti-osteosarcoma activity. Molecular regulators of both apoptosis and the cell cycle should be closely studied as possible mediators for PEDF in osteosarcoma.

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² Ek, E.T., C.R. Dass, and P.F. Choong, *PEDF: a potential molecular therapeutic target with multiple anti-cancer activities*. Trends Mol Med, 2006. **12**(10): p. 497-502.

Doxorubicin anti-osteosarcoma efficacy improved by microencapsulation

Tan, ML, Dunstan DE, Broadhead ML, Friedhuber AM, Choong PFM, Dass CR

Introduction:

Osteosarcoma is the most common primary tumour of bone in children and adolescents. Chemotherapy has a 10-year disease-free survival of approximately 60%. Doxorubicin (Dox) causes various side-effects in patients, especially at the high doses required for tumour control. This study aimed to improve the efficacy of Doxorubicin by microencapsulation.

Methods:

For optimisation of this chitosan/dextran sulphate (DS)-based formulation, molecular weight of DS, concentration of DS, concentration of Dox, and formulation buffer pH were variables tested. Particles were characterised biophysically with electron microscopy, dynamic light scattering, and surface charge determination. The potencies of the Dox-micro particles were gauged in vitro with trypan blue and TUNEL assay. The stability of the best particle was tested at different temperatures and in serum. Particles were tested in two different clinically-relevant disease models, using a clinically-adoptable dosing regimen. Free Dox was also administered to mice bearing orthotopic tumours for comparison.

Results:

Through Dox encapsulation, novel Dox microparticles (DMPs) with a high Dox payload (> 99%) were formed. Multiple optimisation steps produced DMPs which caused osteosarcoma cell death through modes of cell death including apoptosis, and possibly necrosis and autophagy. Treatment of mice bearing orthotopic osteosarcoma with DMP decreased tumour volume, decreased osteolysis, and reduced metastasis to the lungs. DMP-treated mice did not lose weight and no adverse effects on skin, gut lining and heart were noted histologically.

Conclusions:

DMP may be a useful platform clinically provided further studies are performed to validate this technology.

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Pigment Epithelium-Derived Factor (PEDF) – a dose-reducing agent for Doxorubicin in osteosarcoma treatment

Broadhead ML, Dass CR, Choong PFM

Introduction:

Current treatment regimes for high-grade osteosarcoma combine surgery and chemotherapy. The metastatic ability of osteosarcoma remains a great challenge as 25-50% of patients with initially non-metastatic disease develop metastases despite treatment. Neo-adjuvant and adjuvant chemotherapy aim to eliminate micro-metastases present at the time of diagnosis. However, these agents are associated with significant morbidity and risks to the patient. Here we examine the anti-angiogenic Pigment Epithelium-Derived Factor (PEDF) as a potential dose-reducing agent for Doxorubicin in the treatment of osteosarcoma.

Methods:

Two osteosarcoma cell lines, SaOS-2 and SJSA-1, were seeded in 96-well plates. The following day these cell lines were treated with 5nM Doxorubicin, 100nM PEDF or 200nM PEDF. On day 3, CellTitre-Blue reagent and a microplate reader were used to evaluate cell proliferation. Further experiments using the same protocol were then performed with combinations of 0nM, 5nM, 50nM Doxorubicin and 0nM, 100nM, 200nM PEDF.

Results:

Treatment with 5nM Doxorubicin alone did not result in a statistically significant reduction in either SaOS-2 or SJSA-1. However the addition of 200nM PEDF to 5nM Doxorubicin treatment resulted in a 76%($p<0.005$) reduction in SaOS-2 number, while 100nM PEDF added to 5nM Doxorubicin saw a 51%($p<0.05$) reduction in SJSA-1. When these combined treatments were then compared to an increased Doxorubicin (50nM) concentration alone, no statistical significance was demonstrated.

Conclusions:

A synergistic relationship between Doxorubicin and PEDF may exist, suggesting that PEDF could be used as a dose-reducing agent. Cell proliferation assay results support the further study of combined Doxorubicin/PEDF therapy for osteosarcoma.

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The Litigation Threat to Surgical Practice

Smith, J. W.

Introduction

There exists a considerable body of literature, across jurisdictions in the common law world, and including a wide variety of sources – from academic articles to presidential speeches – asserting the existence of a “medical litigation crisis”. Surgery, in particular, is on the “front line” of this crisis, making it also a “surgical litigation crisis”. More recent papers have expressed alarm at the alleged increase in obstetric litigation especially regarding a conjectural cause of cerebral palsy and litigation fears and costs now are the primary reasons for obstetricians avoiding or retiring from obstetric practice.

Methods

The research aims to first understand the nature and the extent of the threat that litigation poses to surgical practice, through examining a number of fields of surgery. A critique of tort law in relation to surgical practice will be undertaken. A synthesis of the literature on the reform of tort law and medical malpractice law will be given including: no-fault medical injury claim systems; limitation of remuneration for non-economic loss and the establishment of special health courts.

Results

J. W. Smith and Professor G. Maddern have signed a contract for a book with Edwin Mellen Press on this topic.

Conclusion

The research work and its publications will propose potential solutions to these litigation problems investigate impediments to their realisation and examine practical strategies for the motivation of governments to engage in legislative reform.

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