BASL: Posters
Wednesday 7th September 2011
Clinical hepatology

P01 THE EFFECT OF INTRAOPERATIVE N-ACETYLCYSTEINE ON HEPATOCELLULAR INJURY DURING LAPAROSCOPIC BARIATRIC SURGERY: A RANDOMISED CONTROLLED TRIAL

doi:10.1136/gutjnl-2011-300857a.1

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Introduction The combination of pneumoperitoneum and intra-operative retraction of the left lobe of the liver leads to hepatocellular injury during laparoscopic oesophago-gastric surgery, with often more than a sixfold rise in serum transaminases. Fatty livers are more susceptible to ischaemic insults and increased oxidative stress.

Aim The aim of the study was to investigate whether the anti-oxidant N-acetylcysteine (NAC) could reduce liver injury during laparoscopic sleeve gastrectomy.

Method Patients undergoing laparoscopic sleeve gastrectomy were allocated to receive intraoperative NAC infusion or standard anaesthetic treatment in a single blind randomised controlled trial. Blood samples were taken before and at the end of surgery and on post-operative days 1–4. Primary endpoints included serum aminotransferases and clinical outcomes. Secondary measures were markers of oxidative stress (superoxide dismutase, lipid peroxidation (TBARS) and liver injury (cytokeratin-18 M30 and M65) and plasma TRAIL and FasL for apoptosis.

Results 20 patients (14 females, median age 44 (27–64) years, median BMI 62 (39–83) kg/m^2) were recruited; NAC n=10, control n=10. Demographic parameters and baseline liver function were similar [pre-op ALT NAC median 25 U/ml (IQR 24–42) vs control 30.5 (29–44)]. The peak rise in liver enzymes was on day 1, but the levels were not significantly different between the groups. ALT: NAC median 126 (IQR 73–627) vs control 136 (107–239); AST: NAC 130 IU/l (68–504) vs Control 124 (72–237). There were no significant differences in day 1 superoxide dismutase (NAC 0.48 pg/ml vs Control 0.66), TBARS (NAC 8.84 nmol/ml vs Control 12.47), CK18-M30 (NAC 340U/l vs 471) and CK18-M65 (NAC 803.5 U/l vs 878). There was a significant reduction in TRAIL and FasL after POD1 (TRAIL pre-op 100.6 pg/ml day 138.8, p<0.01; FasL pre-op 94.6 pg/ml vs POD1 67.5, p<0.01), but there were no significant differences between the treatment groups. Rates of complications and length of stay were not significantly different.

Conclusion NAC was not shown reduce intraoperative liver injury in this small number of patients. The heterogenous nature of the bariatric patient population, with differences in comorbidities, body mass index and intra-abdominal anatomy, makes this difficult. Significant hepatocyte injury does occur through both necrosis and apoptosis, which does not appear to be mediated by TRAIL or FasL.

P02 APOPTOSIS IN PARACETAMOL-INDUCED ACUTE LIVER FAILURE: IMPORTANCE OF EXTRA-HEPATIC ORGAN DYSFUNCTION

doi:10.1136/gutjnl-2011-300857a.2

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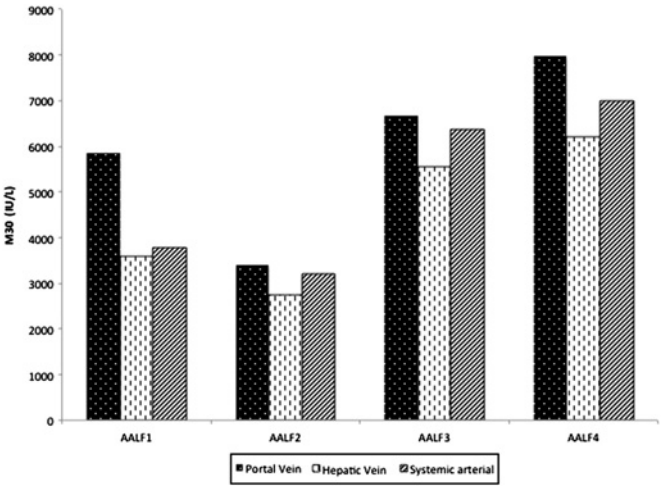
Introduction Both necrotic and apoptotic hepatocyte death pathways have been implicated in paracetamol induced ALF (PALF). Elevated circulating levels of M30, a marker of caspase-3 activation, have been demonstrated in this condition and are postulated to reflect hepatocellular apoptosis. This novel marker has also been reported to have clinical utility as a prognostic indicator in ALF. However, published results are conflicting and it remains unclear whether significant hepatocyte apoptosis is clinically relevant in PALF.

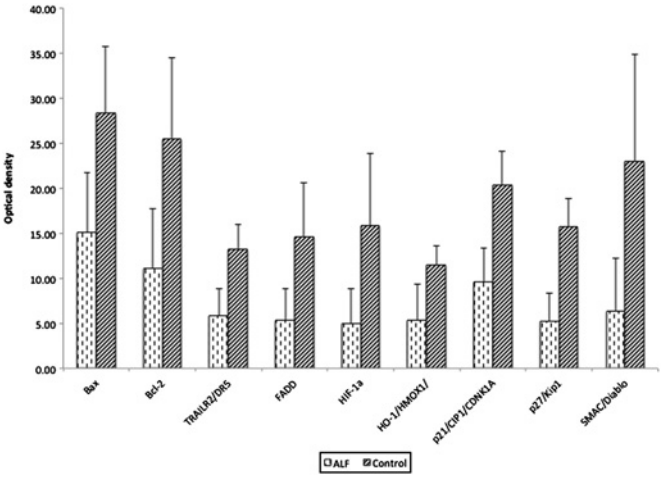


Abstract P02 Figure 1 Regional levels of M30 (marker of cleaved cytokeratin-18) in four cases of Paracetamol-induced acute liver failure.

Aim To investigate the role of hepatocyte apoptosis in PALF.

Method Serum M30 levels were quantified by ELISA (Peviva, Bromma, Sweden) in 62 patients with PALF (34 spontaneous survivors (S) and 28 OLT or died (D)). Control groups of 10 healthy volunteers and 20 chronic HCV patients were used for comparison. Clinical outcome measures in PALF were correlated with M30 levels. In four patients undergoing transplantation for PALF, blood was sampled from the hepatic vein (HV), portal vein (PV) and a systemic artery and serum levels of M30 quantified as above. A focused proteome apoptosis array was performed on liver homogenates from 4 PALF cases and 4 controls. Protein was quantified using a modified Lowry assay and concentrations normalised. Array films were scanned and analysed in ImageJ. H&E stained liver sections from AALF patients were examined for histological evidence of apoptosis.

Results Serum M30 levels were significantly elevated in PALF (3970 IU/l) compared with both healthy volunteers (144 IU/l) and HCV patients (170 IU/l) (p<0.001). Serum levels of M30 were significantly elevated in PALF-D compared to PALF-S (5199 vs 2357 IU/l; p<0.0005). There was a transportal gradient of M30 in all patients tested, with highest levels in the PV and lowest in the HV



Abstract P02 Figure 2 Downregulation of apoptosis-associated proteins in AALF patients (n=4) compared with controls (n=4).

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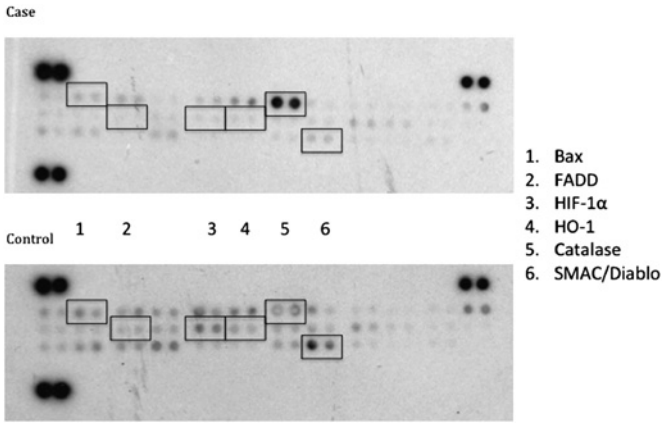

Abstract P02 Figure 3 Examples of apoptosis array for case and control.

($p<0.03$). Systemic arterial M30 levels were intermediate between the PV and HV levels (Abstract P02 figure 1). Analysis of apoptosis arrays showed significant downregulation of a number of apoptosis-associated proteins, including Bax, HIF-1, FADD and SMAC/Diablo ($p<0.04$) (Abstract P02 figure 2). Catalase was markedly elevated compared to controls in three of the four AALF patients. Histological evaluation revealed confluent hepatocellular loss, epithelial regenerative activity and an absence of apoptotic bodies.

Conclusion In this large cohort of PALF patients we have demonstrated the presence of elevated M30 levels and a correlation between caspase three activation and poor clinical outcome. The transhepatic M30 gradient, down regulation of apoptosis-associated proteins and histological appearances indicate that hepatocellular apoptosis might not be the major source of circulating M30. Our data also indicate that in established PALF, apoptosis in non-hepatic epithelial tissues may predominate and is likely to reflect incipient multi-organ failure, with resulting poor outcomes.

P03 THE DIAGNOSTIC VALUE OF TRANSIENT ELASTOGRAPHY COMPARED TO CLINICAL ACUMEN, LABORATORY TESTS AND ULTRASOUND? IS THERE ADDED VALUE?

doi:10.1136/gutjnl-2011-300857a.3

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Introduction The diagnostic performance of transient elastography (TE), and other non-invasive biomarkers of fibrosis, is assessed by direct comparison with liver biopsy. However clinical acumen, laboratory tests and ultrasonography are utilised for the assessment of fibrosis in clinical practice.

Aim The aim of this study was to assess the incremental value of elastography compared to routine diagnostic tools.

Method We included consecutive patients with both fibroscan and biopsy data. Patients with decompensated cirrhosis or suboptimal fibroscan readings were excluded (success rate <60% or IQR/median >0.21). Four consultant/attending hepatologists (who were blinded to TE and biopsy results) were asked to assess the severity of fibrosis on the basis of anonymised clinical data. Simple laboratory tests (eg, full blood count, liver function tests and clotting) and ultrasonography for each case were then given to the clinicians to assess the incremental increase in diagnostic performance. One independent pathologist formally assessed the degree of fibrosis on biopsy, which was the reference standard. Receiver Operating Characteristics (ROC) curves were calculated for (1) clinical acumen (2) clinical acumen + laboratory tests + ultrasonography and (3) TE, for the prediction of significant fibrosis (greater or equal to F2) and cirrhosis.

Results 130 patients were enrolled in the study with paired data and a biopsy deemed adequate for staging. The cohort (65% male; mean age 46 years) was of mixed aetiology (15% ALD, 48% chronic viral hepatitis, 24% NAFLD, 24% other). The average biopsy length was 23 mm with 16 portal tracts. The median TE reading was 6.3 (median IQR 0.8 and 100% success rate).

Conclusion There appears to be little additional benefit in AUC performance of transient elastography to diagnose cirrhosis compared to clinical acumen and routinely available tests. There is however incremental diagnostic benefit for the assessment of significant fibrosis. The baseline performance of simple diagnostic tools, which will vary depending on the stage of fibrosis, needs to be accounted for when assessing liver biomarker performance.

P04 A DOSE EFFECT OF THE DISEASE RISK GENE HLA DR3 CONTRIBUTES TO NUMERICAL AND FUNCTIONAL IMPAIRMENT OF CD4+CD25+ REGULATORY T CELLS IN PATIENTS WITH AUTOIMMUNE HEPATITIS

doi:10.1136/gutjnl-2011-300857a.4

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Introduction Autoimmune diseases are frequent among first degree relatives (FDR) of patients with autoimmune hepatitis (AIH), but concordance for AIH is rare. A numerical and functional impairment of $CD4^{pos}CD25^{pos}$ regulatory T cells (Tregs) is described in AIH patients, but no study has addressed Treg status in their FDR.

Aim To define whether the defect of Tregs in AIH is inherited and is associated with disease predisposing HLA genes.

Abstract P03 Table 1 AUC performance for the assessment of significant fibrosis and cirrhosis

	Clinician	Clinical acumen AUC	Clinical acumen/lab tests/radiology AUC	TE alone AUC	p Value for AUC of TE vs clinical/lab/radiology*
Detection of significant fibrosis	1	0.56	0.55	0.78	0.0003
	2	0.52	0.56	0.81	0.0001
	3	0.56	0.53	0.87	<0.0001
	4	0.59	0.52	0.78	<0.0001
Detection of cirrhosis	1	0.63	0.70	0.87	0.0268
	2	0.65	0.73	0.82	0.6693
	3	0.77	0.77	0.89	0.1367
	4	0.65	0.80	0.84	0.6705

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