

ABSTRACT FROM CURRENT LITERATURE

A Randomized Trial of Intravenous Alteplase before Endovascular Treatment for Stroke LeCouffe NE, Kappelhof M, Treurnie K.M, et al

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Background: The value of administering intravenous alteplase before endovascular treatment (EVT) for acute ischemic stroke has not been studied extensively, particularly in non-Asian populations.

Methods : We performed an open-label, multicenter, randomized trial in Europe involving patients with stroke who presented directly to a hospital that was capable of providing EVT and who were eligible for intravenous alteplase and EVT. Patients were randomly assigned in a 1:1 ratio to receive EVT alone or intravenous alteplase followed by EVT (the standard of care). The primary end point was functional outcome on the modified Rankin scale (range, 0 [no disability to 6 [death]] at 90 days. We assessed the superiority of EVT alone over alteplase plus EVT, as well as no inferiority by a margin of 0.8 for the lower boundary of the 95% confidence interval for the odds ratio of the two trial groups. Death from any cause and symptomatic intracerebral hemorrhage were the main safety end points.

Results : The analysis included 539 patients. The median score on the modified Rankin scale at 90 days was 3 (interquartile range, 2 to 5) with EVT alone and 2 (inter- quartile range, 2 to 5) with alteplase plus EVT. The adjusted common odds ratio was 0.84 (95% confidence interval [CI], 0.62 to 1.15; P=0.28), which showed neither superiority nor noninferiority of EVT alone. Mortality was 20.5% with EVT alone and 15.8% with alteplase plus EVT adjusted odds ratio, 1.39; 95% CI 0.84 to 2.30). Symptomatic intracerebral hemorrhage occurred in 5.9% and 5.3% of the patients in the respective groups (adjusted odds ratio, 1.30, 95% CI 0.60 to 2.81).

Conclusions: In a randomized trial involving European patients, EVT alone was neither superior nor noninferior to intravenous alteplase followed by EVT with regard to disability outcome at 90 days after stroke. The incidence of symptomatic intracerebral hemorrhage was similar in the two groups. (Funded by the Collaboration for New Treatments of Acute Stroke consortium and others; MR CLEAN-NO IV ISRCTN number, ISRCTN80619088.)

Early Convalescent Plasma for High-Risk Outpatients with Covid-19 Korley FK, Durkalski-Mauldin V, Yeatts SD, et al

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Background: Early administration of convalescent plasma obtained from blood donors

who have recovered from coronavirus disease 2019 (Covid-19) may prevent disease progression in acutely ill, high-risk patients with Covid-19.

Methods: In this randomized, multicenter, single-blind trial, we assigned patients who were being treated in an emergency department for Covid-19 symptoms to receive either one unit of convalescent plasma with a high titer of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or placebo. All the patients were either 50 years of age or older or had one or more risk factors for disease progression. In addition, all the patients presented to the emergency department within 7 days after symptom onset and were in stable condition for outpatient management. The primary outcome was disease progression within 15 days after randomization, which was a composite of hospital admission for any reason, seeking emergency or urgent care, or death without hospitalization. Secondary outcomes included the worst severity of illness on an 8-category ordinal scale, hospital-free days within 30 days after randomization, and death from any cause.

Results: A total of 511 patients were enrolled in the trial (257 in the convalescent-plasma group and 254 in the placebo group). The median age of the patients was 54 years; the median symptom duration was 4 days. In the donor plasma samples, the median titer of SARS-CoV-2 neutralizing antibodies was 1:641. Disease progression occurred in 77 patients (30.0%) in the convalescent-plasma group and in 81 patients (31.9%) in the placebo group (risk difference, 1.9 percentage points; 95% credible interval, -6.0 to 9.8; posterior probability of superiority of convalescent plasma, 0.68). Five patients in the plasma group and 1 patient in the placebo group died. Outcomes regarding worst illness severity and hospital-free days were similar in the two groups.

Conclusions: The administration of Covid-19 convalescent plasma to high-risk outpatients within 1 week after the onset of symptoms of Covid-19 did not prevent disease progression. (SIREN-C3PO Clinical Trials.gov number, NCT04355767.)

Study of mirtazapine for agitated behaviours in dementia (SYMBAD): a randomised, double-blind, placebo-controlled trial

Banerjee S, High J, Stuting S, et al.

Lancet 2021; 398: 1487-97

Background: Agitation is common in people with dementia and negatively affects the quality of life of both people with dementia and carers. Non drug patient centre care is the first-line treatment, but there is a need for other treatment when this care is not effective. Current evidence is sparse on safe and effective alternatives to antipsychotics. We assessed the efficacy and safety of mirtazapine, an antide

pressant prescribed for agitation in dementia.

Methods: This parallel-group, double-blind, placebo-controlled trial-the Study of Mirtazapine for Agitated Behaviours in Dementia trial (SYMRAD) was done in 26 UK centres. Participants had probable or possible Alzheimer's disease, agitation unresponsive to non-drug treatment, and a Cohen-Mansfield Agitation Inventory (CMAI) score of 45 or more. They were randomly assigned (1:1) to receive either mirtazapine (titrated to 45 mg) or placebo. The primary outcome was reduction in CMAI score at 12 weeks. This trial is registered with ClinicalTrials.gov, NCT03031184, and ISRCTN17411897.

Findings: Between Jan 26, 2017, and March 6, 2020, 204 participants were recruited and randomised. Mean CMAI scores at 12 weeks were not significantly different between participants receiving mirtazapine and participants receiving placebo (adjusted mean difference -1.74, 95% CI -7.17 to 3.69; $p=0.53$). The number of controls with adverse events (65 [64%] of 102 controls) was similar to that in the mirtazapine group (67 [66%] of 102 participants receiving mirtazapine). However, there were more deaths in the mirtazapine group (6-7) by week 16 than in the control group (n-1), with post-hoc analysis suggesting this difference was of marginal statistical significance ($p=0.065$).

Interpretation: This trial found no benefit of mirtazapine compared with placebo, and we observed a potentially higher mortality with use of mirtazapine. The data from this study do not support using mirtazapine as a treatment for agitation in dementia

Redefining B-blocker response in heart failure patients with sinus rhythm and atrial fibrillation: a machine learning cluster analysis

Karwath A, Bunting KV, Gill S.K, et al
Lancet 2021; 398:1427-35

Background: Mortality remains unacceptably high in patients with heart failure and reduced left ventricular ejection fraction (LVEF) despite advances in therapeutics. We hypothesised that a novel artificial intelligence approach could better assess multiple and higher dimension interactions of comorbidities, and define clusters of B-blocker efficacy in patients with sinus rhythm and atrial fibrillation.

Methods: Neural network-based variational autoencoders and hierarchical clustering were applied to pooled individual patient data from nine double-blind, randomised, placebo-controlled trials of blockers. All cause mortality during median 13 years of follow-up was assessed by intention to treat, stratified by electrocardiographic heart rhythm. The number of clusters and dimensions was determined objectively, with results validated using leave-one trial out approach. This study was prospectively registered with ClinicalTrials.gov (NCT00832442)

and the PROSPERO database of Systematic reviews (CRD42014010012)

Findings: 15659 patients with heart failure and LVEF of less than 50% were included, with median age 65 years (IQR 56-72) and LVEF 27% (IQR 21-33). 3708 (24%) patients were women. In sinus rhythm (n=12822), most cluster demonstrated a consistent overall mortality benefit from B blockers, with odds ratios (OR) ranging from 0.54 to 0.74. One cluster in sinus rhythm of older patients with less severe symptoms showed no significant efficacy (OR 0.86, 95% CI 0.67-1.10; $p=0.22$). In atrial fibrillation (n=2837), four of five clusters were consistent with the overall neutral effect of B blockers versus placebo (OR 0.92, 0.77-1.10 $p=0.37$). One cluster of younger atrial fibrillation patients at lower mortality risk but similar LVEF to average had a statistically significant reduction in mortality with B blocker (OR 0.57, 0.35-0.93, $p=0.023$). The robustness and consistency of clustering was confirmed for all models ($p<0.0001$ vs random), and cluster membership was externally validated across the nine independent trials.

Interpretation: An artificial intelligence-based clustering approach was able to distinguish prognostic response from B blockers in patients with heart failure and reduced LVEF. This included patients in sinus rhythm with suboptimal efficacy, as well as a cluster of patients with atrial fibrillation where B blockers did reduce mortality.

Adjuvant corticosteroids for prevention of kidney scarring in children with acute pyelonephritis: a systematic review and meta-analysis

Meena J, Kumar J

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DOI: 10.1136/archdischild-2020-320591

Background: Acute pyelonephritis in children may result in permanent kidney scarring that is primarily caused by inflammation during acute infection. Antibiotic therapy alone is not enough to significantly reduce kidney scarring, and adjuvant corticosteroid therapy has shown a significant reduction in inflammatory cytokines in urine prompting its evaluation in randomised controlled trials. A few clinical trials showed a trend towards a reduction in renal scarring but did not have an adequate sample size to show a significant effect. Therefore, we planned to synthesise the available evidence on the role of corticosteroids as adjuvant therapy in reducing kidney scarring.

Objective: to assess the efficacy and safety of adjuvant corticosteroid therapy for the prevention of kidney scarring in children with acute pyelonephritis.

Design: Systematic review and meta-analysis.

Setting: Community-acquired febrile urinary tract infections.

Patients: Children (less than 18 years) with acute pyelonephritis.

Intervention: Adjuvant corticosteroid therapy (along with antibiotic treatment)

Main outcome measures: Primary: efficacy in preventing kidney scarring; secondary: serious adverse events associated with corticosteroid therapy.

Results: Three randomised trials (529 children) were included. Corticosteroids are effective in lowering the risk of kidney scarring as compared with placebo (risk ratio (RR): 0.57; 95% CI 0.36 to 0.90). No significant increase risk of bacteraemia (RR: 1.38; 95% CI 0.23 to 8.23) and hospitalisation (RR: 0.87; 95% CI 0.3 to 2.55) was observed in corticosteroid group.

Conclusion: Moderate quality evidence suggests that short duration 'adjuvant corticosteroid therapy' along with routine antibiotic therapy in acute febrile urinary tract infection significantly reduces the risk of kidney scarring without any significant adverse effects.

Hyponatraemia despite isotonic maintenance fluid therapy: a time series intervention study

Chromek M, Jungner A, Rudolfson N, et al

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Objective: To examine the prevalence of dysnatraemias among children admitted for paediatric surgery before and after a change from hypotonic to isotonic intravenous maintenance fluid therapy

Design: Retrospective consecutive time series intervention study.

Setting: Paediatric surgery ward at the Children's Hospital in Lund, during a 7-year period, 2010-2017

Patients: All children with a blood sodium concentration measurement during the study period were included. Hypotonic maintenance fluid (40 mmol/l NaCl and 20 mmol/l KCl) was used during the first 3 years of the study (646 patients), and isotonic solution (140 mmol/l NaCl and 20 mmol/l KCl) was used during the following period (807 patients).

Main outcome measures: Primary outcomes were sodium concentration and occurrence of hyponatraemia (<135 mmol/L) or hypernatraemia (>145 mmol/L).

Results: Overall, the change from hypotonic to isotonic intravenous maintenance fluid therapy was associated with a decreased prevalence of hyponatraemia from 29% to 22% (adjusted OR 0.65 (0.51-0.82)) without a significantly increased odds for hypernatraemia (from 3.4% to 4.3%, adjusted OR 1.2 (0.71-2.1)). Hyponatraemia <130 mmol/L decreased from 6.2% to 2.6%, and hyponatraemia <125 mmol/L decreased from 2.0% to 0.5%

Conclusions: Routine use of intravenous isotonic maintenance fluids was associated with lower prevalence of hyponatraemia, although hyponatraemia still occurred in over 20% of patients. We propose that the composition and the

volume of administered fluid need to be addressed.

Axillary evaluation in ductal cancer in situ of the breast: challenging the diagnostic accuracy of clinical practice guidelines

Karakatsanis A, Charalampoudis P, Pistioli L et al

BJS: 2021; 108: 1120-1125,

DOI: org/10.1093/bjs/znab149

Background: Staging of the axilla is not routine in ductal cancer in situ (DCIS) although invasive cancer is observed in 20-25 per cent of patients at final pathology. Upfront sentinel lymph node dissection (SLND) is advocated in clinical practice guidelines in certain situations. These include expected challenges in subsequent SLN detection and when the risk for invasion is high. Clinical practice guidelines are, however, inconsistent and lead to considerable practice variability.

Methods: Clinical practice guidelines for upfront SLND in DCIS were identified and applied to patients included in the prospective SentiNot study. These patients were evaluated by six independent, blinded raters. Agreement statistics were performed to assess agreement and concordance. Receiver operating characteristic curves were constructed, to assess guideline accuracy in identifying patients with underlying invasion.

Results: Eight guidelines with relevant recommendations were identified. Interobserver agreement varied greatly (kappa: 0.23-0.9) and the interpretation as to whether SLND should be performed ranged from 40-90 per cent and with varying concordance (32-88 per cent). The diagnostic accuracy was low with area under the curve ranging from 0.45 to 0.55. Fifty to 90 per cent of patients with pure DCIS would undergo unnecessary SLNB, whereas 10-50 per cent of patients with invasion were not identified as 'high risk'. Agreement across guidelines was low (kappa = 0.24), meaning that different patients had a similar risk of being treated inaccurately.

Conclusion: Available guidelines are inaccurate in identifying patients with DCIS who would benefit from upfront SLNB. Guideline refinement with detailed preoperative work-up and novel techniques for SLND identification could address this challenge and avoid overtreatment.

Completion pancreatectomy or a pancreas-preserving procedure during relaparotomy for pancreatic fistula after pancreatoduodenectomy: a multicentre cohort study and meta-analysis

Groen JV, Smits FJ, Koole D et al

BJS: 2021, 108: 1371-1379,

DOI: org/10.1093/bjs/znab273

Background: Despite the fact that primary percutaneous catheter drainage has become standard practice, some patients with pancreatic fistula after pancreatoduodenectomy ultimately undergo a relaparotomy. The aim of this study was to compare completion pancreatectomy with a pancreas-preserving procedure in patients undergoing relaparotomy for pancreatic fistula after pancreatoduodenectomy.

Methods: This retrospective cohort study of nine institutions included patients who underwent relaparotomy for pancreatic fistula after pancreatoduodenectomy from 2005-2018. Furthermore, a systematic review and meta-analysis were performed according to the PRISMA guidelines.

Results: From 4877 patients undergoing pancreatoduodenectomy, 786 (16 per cent) developed a pancreatic fistula grade B/C and 162 (3 per cent) underwent a relaparotomy for pancreatic fistula. Of these patients, 36 (22 per cent) underwent a completion pancreatectomy and 126 (78 per cent) a pancreas-preserving procedure. Mortality was higher after completion pancreatectomy (20 (56 per cent) versus 40 patients (32 per cent); $P=0.009$), which remained after adjusting for sex, age, BMI, ASA score, previous reintervention, and organ failure in the 24 h before relaparotomy (adjusted odds ratio 2.55, 95 per cent c.i. 1.07 to 6.08). The proportion of additional reinterventions was not different between groups (23 (64 per cent) versus 84 patients (67 per cent); $P=0.756$). The meta-analysis including 33 studies evaluating 745 patients, confirmed the association between completion pancreatectomy and mortality (Mantel-Haenszel random-effects model: odds ratio 1.99, 95 per cent c.i. 1.03 to 3.84).

Conclusion: Based on the current data, a pancreas-preserving procedure seems preferable to completion pancreatectomy in patients in whom a relaparotomy is deemed necessary for pancreatic fistula after pancreatoduodenectomy.

Adnexectomy by vaginal Natural Orifice Transluminal Endoscopic Surgery versus laparoscopy: results of a first randomised controlled trial (NOTABLE trial)

Baekelandt J, Mulder PAD, Roy IL, et al

BJOG 2021;128:1782-1791

DOI: 10.1111/1471-0528.16838.

Objective: To compare adnexectomy by vaginal Natural Orifice Transluminal Endoscopic Surgery (VNOTES) versus laparoscopy.

Design: Parallel group, 1:1 single-centre single-blinded randomised trial, designed as non-inferiority study with a margin of 15%.

Setting: Belgian teaching hospital.

Population : Non-pregnant non-virgin women with an intact uterus and without obliteration of the pouch of Douglas scheduled to undergo removal of an adnexal mass assessed to be benign on ultrasound by IOTA criteria.

Methods: Randomisation to laparoscopy (control group) or NOTES (experimental group). Stratification according to adnexal size. Blinding of participants and outcome assessors by sham incisions.

Main outcome measures: The primary outcome measure was adnexectomy by the allocated technique. Secondary outcomes included duration of surgery, pain scores and analgesics used, quality of life and adverse events.

Results : We randomly assigned 67 participants (34 to the VNOTES group and 33 to the laparoscopy group). The primary end point was always reached in both groups: there were no conversions. We performed a sensitivity analysis for the primary outcome, assuming one conversion in the VNOTES group and no conversions in the laparoscopy group: the one-sided 95% upper limit for the differences in proportions of conversion was estimated as 13%, which is below the predefined non-inferiority margin of 15%. The secondary outcomes demonstrated a shorter duration of surgery, lower pain scores, lower total dose of analgesics and a trend for more adverse events in the VNOTES group.

Conclusions: vNOTES is non-inferior to laparoscopy for a successful adnexectomy without conversion.

The effect of mode of delivery and duration of labour on subsequent pregnancy outcomes: a retrospective cohort study

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Objective: To assess whether delivery mode and duration of labour in a first labour of spontaneous onset is associated with gestational length, delivery mode and neonatal outcome in the subsequent pregnancy.

Study design: Retrospective analysis of prospectively collected data.

Setting: 15 Maternity units in North West London (1988-2000).

Population: 30 840 women with spontaneous onset of labour in pregnancy 1 and a subsequent birth reported in the same database.

Methods: Assessment of outcomes by mode of delivery in pregnancy 1, restricting the analysis to the difference in the gestational length between pregnancy 1 and 2.

Main outcome measures: Gestational length, mode of delivery and neonatal unit admission in pregnancy 2.

Results: Caesarean section (CS) in the first or second stage of labour in pregnancy 1 was associated with pregnancy 2 being a median of 5 and 8 days shorter and a preterm birth rate of 6.0% and 10.1%, respectively, whereas following a normal or instrumental vaginal birth in pregnancy 1, the median duration was similar, with preterm delivery rates of 4.5% and 3.9%. In all, 56.2% of women with a CS in pregnancy 1 had a repeat CS and 12.5% of their babies were admitted to a neonatal unit, compared with 5.3% of women with vaginal birth. Longer labours were associated with shorter gestations in pregnancy 2.

Conclusions: Compared with vaginal birth, an emergency CS in the first-term pregnancy is associated with a shorter gestational length, increased rate of repeat CS and increased risk of NNU admission in the next pregnancy.