Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis

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EDITORIAL by Prowle and Pearse

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Cite this as: *BMJ* 2013;346:f839
doi: 10.1136/bmj.f839

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f839'

STUDY QUESTION

What are the effects of fluid therapy with hydroxyethyl starch (HES) 130/0.38-0.45 versus crystalloid or albumin on mortality, kidney injury, bleeding, and serious adverse events in patients with sepsis?

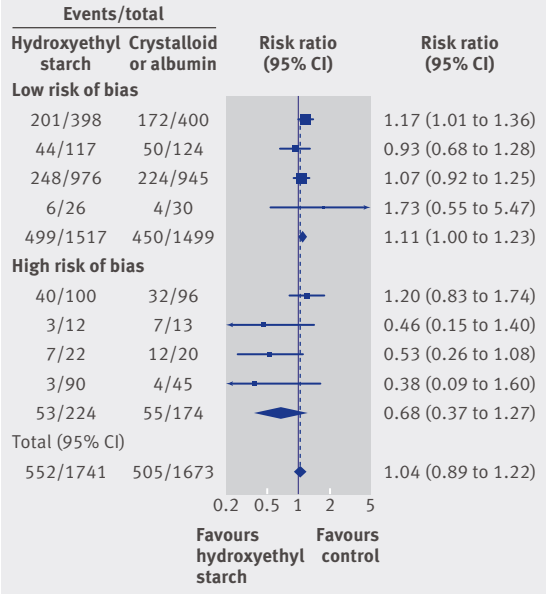
SUMMARY ANSWER

In meta-analyses of trials with low risk of bias, HES 130/0.38-0.45 versus crystalloid or albumin may have increased mortality in patients with sepsis. The use of renal replacement therapy and red blood cells and the occurrence of serious adverse events were clearly increased with HES, and it seems unlikely that HES provides overall clinical benefit for patients with sepsis.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

HES 130/0.38-045 is the most commonly used colloid worldwide, but its safety and efficacy have not been established in patients with sepsis. This study pooled the results of existing randomised clinical trials and showed that treatment with HES increased the risk of having renal replacement therapy, transfusion with red blood cells, and serious adverse events.

All cause mortality in relation to risk of bias in trials



Selection criteria for studies

We searched the Cochrane library, Medline, Embase, Biosis previews, Science Citation Index, and Cumulative Index to Nursing and Allied Health Literature from 1995 to September 2012. Additional trials were sought from reference lists, other reviews, online trial registration databases, and manufactures of HES. We included randomised clinical trials comparing HES 130/0.38-45 with crystalloid or albumin in patients with sepsis. If patients with sepsis constituted a subgroup of the trial population, we included the trial only if the randomisation was stratified for sepsis or the trial included more than 500 patients with sepsis. Trials were included irrespective of language, publication status, and reported outcomes. We pooled the trial results in conventional meta-analysis and adjusted the meta-analyses with trial sequential analysis (TSA)—a sensitivity analysis that widens the confidence interval in case data are too sparse from which to draw firm conclusions.

Primary outcome

All cause mortality.

Main results and role of chance

Nine trials randomising 3456 patients with sepsis were included. Overall, HES 130/0.38-0.45 versus crystalloid or albumin did not affect the relative risk of death (1.04, 95% confidence interval 0.89 to 1.22), but in the predefined analysis of trials with low risk of bias the relative risk of death was 1.11 (1.00 to 1.23, TSA adjusted 95% confidence interval 0.95 to 1.29). More patients in the HES group received renal replacement therapy (1.36, 1.08 to 1.72, TSA adjusted 1.03 to 1.80) and the relative risk of acute kidney injury was 1.18 (0.99 to 1.40, TSA adjusted 0.90 to 1.54). More patients in the HES group were transfused with red blood cells (1.29, 1.13 to 1.48, TSA adjusted 1.10 to 1.51) and more patients had serious adverse events (1.30, 1.02 to 1.67, TSA adjusted 0.93 to 1.83). The transfused volume of red blood cells did not differ between the groups.

Bias, confounding, and other reasons for caution

Interpretation of the effects of HES 130/0.38-0.45 was complicated owing to trials of low quality, short follow-up, and poor outcome reporting. However, recent large, well designed trials showed signs of harm without statistical heterogeneity.

Study funding/potential competing interests

This study received no funding. AP, NH, JW, and MS have conducted public funded trials of HES. These trials received study drugs from B Braun Melsungen and Fresenius Kabi free of charge. AP and NH's department receives research funds from Fresenius Kabi.

Use of caffeinated substances and risk of crashes in long distance drivers of commercial vehicles: case-control study

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Cite this as: *BMJ* 2013;346:f1140
doi: 10.1136/bmj.f1140

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f1140

bmj.com

- Research: Awareness of driving while sleepy and road traffic accidents (*BMJ* 2012;344:e536)
- Research: Acute cannabis consumption and motor vehicle collision risk (*BMJ* 2006;333:75)

STUDY QUESTION

Is there an association between the use of substances containing caffeine and the risk of crash in long distance drivers of commercial motor vehicles?

SUMMARY ANSWER

Consuming caffeinated substances for the purpose of staying awake while driving can significantly reduce the risk of a crash.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Long distance drivers of commercial vehicles are at considerable risk of daytime fatigue and are known to use stimulants and substances containing caffeine to stay awake. The effectiveness of caffeine for enhancing alertness during monotonous task performance has previously been demonstrated in laboratory and driving simulator settings. After adjustment for possible confounding factors, consumption of caffeinated substances to assist driving alertness was associated with a reduced risk of crashing among long distance commercial motor vehicle drivers.

Participants and setting

Study participants were long distance drivers of commercial vehicles who were recently involved in a crash attended by police (cases) and control drivers who had not crashed while driving a commercial vehicle in the past 12 months. Drivers were recruited across the states of New South Wales and Western Australia, Australia.

Design, size, and duration

Case-control study, conducted between December 2008 and May 2011. There were 530 case drivers and 517 control drivers.

Primary outcome, risks, exposures

The primary outcome was the likelihood of a crash associated with the use of substances containing caffeine, after adjustment for factors including age, health disorders, sleep patterns, and symptoms of sleep disorders as well as exposures such as distance driven, hours slept, breaks taken, and night driving schedules. Substances containing caffeine included coffee, tea, caffeinated soft drinks, energy drinks containing caffeine, and caffeine tablets. Commercial vehicle driver crashes involving police attendance were reported, confidentially, to the study team on a weekly basis in each state.

Main results and the role of chance

Forty three percent of drivers (162 case drivers and 290 controls) reported consuming substances containing caffeine for the express purpose of staying awake. After adjustment for potential confounders, drivers who consumed caffeinated substances for this purpose had a 63% reduced likelihood of crashing (odds ratio 0.37, 95% confidence interval 0.27 to 0.50) compared with drivers who did not take caffeinated substances.

Bias, confounding, and other reasons for caution

There was potential for state level factors to influence the findings of our study—for example, there are different legislative requirements between the states regulating management practices for work and fatigue in long distance drivers. Such state specific factors could have influenced driver behaviour as well as their recall of behaviour, such as the number of breaks taken, hours driven, and possibly other self reported behaviours. Although we found a distinct difference in consumption of caffeinated substances between case drivers and controls, the validity of the levels of consumption (or dose-response quantification) was subject to reporting bias and therefore was not modelled other than as a binary variable, for which it was deemed robust.

Generalisability to other populations

The finding that the consumption of caffeinated substances can significantly protect against the risk of a crash for long distance drivers has important implications for the improvement of fatigue management strategies for this and similar populations. Further studies are needed to confirm these findings in other settings and to better understand the effects of caffeine relative to other strategies to manage fatigue.

Study funding/potential competing interests

The study was funded by the Australian Research Council, the Australian Government Department of Infrastructure, Transport, Regional Development and Local Government, DiagnoseIT, the National Transport Commission, Queensland Transport, the Roads and Traffic Authority of New South Wales and Main Roads in Western Australia.

Associations between use of stimulant substances and crashes in long distance commercial vehicle drivers who were recently involved in crash (cases) and control drivers who had not crashed in previous 12 months. Figures are numbers (percentage) of participants

	Cases (n=530)	Controls (n=517)	Adjusted* OR (95% CI)
Uses caffeinated stimulant:			
Not†	368 (69.4)	227 (43.9)	1.00
Yes	162 (30.6)	290 (56.1)	0.37 (0.27 to 0.50)
Uses illegal stimulants‡:			
Never†	520 (98.1)	497 (96.1)	1.00
Often/sometimes	10 (1.89)	20 (3.87)	0.68 (0.27 to 1.67)
Previous crash§	119 (22.5)	75 (14.5)	1.81 (1.26 to 2.62)

*Adjusted for age, distance driven, hours of sleep, night driving, and breaks taken and state of crash/recruitment.
†Reference category.
‡Including speed, ecstasy, and cocaine.
§Police attended commercial vehicle driver crash in past five years, not including current crash for cases.

Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases

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Cite this as: *BMJ* 2013;346:f880
doi: 10.1136/bmj.f880

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f880

STUDY QUESTION

What is the effect of high potency statins on the risk of acute kidney injury (AKI), compared with low potency statins?

SUMMARY ANSWER

Use of high potency statins is associated with an increased rate of hospital admissions for AKI relative to the use of low potency statins.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Although signals have indicated a possible harmful effect of statins on the kidney, no studies have specifically looked at acute kidney injury. We quantified this effect with high potency statins.

Participants and setting

We identified all patients aged 40 years or older initiating statin therapy between January 1997 and April 2008 from the administrative healthcare databases of seven Canadian provinces, the United Kingdom Clinical Practice Research Datalink, and the United States Caremark-Medicare database.

Design, size, and duration

Retrospective cohort studies were conducted within each database, with patients initiating treatment with high potency statins compared with patients initiating low potency statins. Patients were followed for up to two years, until admission to hospital for AKI. A nested case-control analysis was performed to assess the on-treatment effect of high potency versus low potency statin use during the first two years of treatment, with each AKI case matched on age, sex, and calendar time with 10 controls randomly selected from the risk set. Conditional logistic regression, adjusted for high dimensional propensity scores (hdPS), estimated rate ratios of AKI hospitalization for three mutually exclusive durations of current exposure to high poten cy statins (≤120, 121-365, and 366-730 days), relative to the same duration of low potency statin use. Each center's results were then combined across sites using meta-analytic methods.

Primary outcome(s), risks, exposures

Hospitalization for AKI associated with current use of high potency versus low potency statins was estimated separately for patients with and without a history of chronic kidney disease (CKD).

Main results and the role of chance

The study included 2 067 639 patients initiating statin therapy, with 24 418 hospitalized for AKI at two year follow-up. Among patients with no history of CKD, current users of high potency statins were 34% more likely than users of low potency statins to be hospitalized for AKI within 120 days of starting treatment (rate ratio 1.34; 95% confidence interval 1.25 to 1.43). No such significant increase was observed among patients with CKD (1.10; 0.99 to 1.23). Sensitivity analyses and tests for hetero-geneity confirmed that this modest association was robust across participating sites (see table).

Bias, confounding, and other reasons for caution

The AKI outcome was defined using a validated algorithm with high specificity but low sensitivity. Thus, the absolute rates of AKI identified in hospitalization records are likely to underestimate the true incidence of the injury defined by changes in serum creatinine levels. However, we do not expect that the case definition resulted in differential misclassification of patients according to the choice of statin potency, thus not affecting the validity of the results. Although every study patient was prescribed a statin and we adjusted for hundreds of potential confounders using hdPS scores, some residual confounding may remain.

Generalisability to other populations

It is reasonable to generalize our results to patients receiving statins aged over 40 years in other countries.

Study funding/potential competing interests

CNODES is a collaborating center of the Drug Safety and Effectiveness Network, funded by the Canadian Institutes of Health Research (grant DSE-111845) who oversaw the peer review and funding process. PE receives consultancy and speaker's fees from Astra Zeneca, Boehringer Ingelheim, Merck, and Nycomed; and a research grant from Boehringer Ingelheim. AL receives consultancy fees from Oxford Outcomes (now Icon), which conducts contracted work for pharmaceutical companies.

As treated analysis of hospitalizations for acute kidney injury

	Low potency statins		High potency statins		
	No of patients admitted	No of controls	No of patients admitted	No of controls	Rate ratio (95% CI)
Patients without chronic kidney disease					
≤120 days of current therapy	2354	26 168	2337	18 599	1.34 (1.25 to 1.43)
>120 to ≤365 days of current therapy	2595	28 716	2242	20 624	1.11 (1.04 to 1.19)
>365 to ≤730 days of current therapy	3316	37 121	2706	23 716	1.15 (1.09 to 1.22)
Past therapy	1947	23 517	1337	14 726	1.06 (0.98 to 1.15)
Patients with chronic kidney disease					
≤120 days of current therapy	940	6851	956	5386	1.10 (0.99 to 1.23)
>120 to ≤365 days of current therapy	787	7590	756	5797	1.08 (0.96 to 1.22)
>365 to ≤730 days of current therapy	787	10 811	697	8197	1.04 (0.92 to 1.18)
Past therapy	381	3840	280	2536	1.15 (0.85 to 1.57)

Accuracy of the "traffic light" clinical decision rule for serious bacterial infections in young children with fever: a retrospective cohort study

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Cite this as: *BMJ* 2013;346:f866
doi: 10.1136/bmj.f866

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;346:f866

bmj.com
- Editorial: Diagnosing serious bacterial infection in young febrile children (*BMJ* 2010;340:c2062)
- Research: The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children (*BMJ* 2010;340:c1594)

STUDY QUESTION

What is the accuracy of the "traffic light" clinical decision rule, with and without urine analysis, for the detection of serious bacterial infections in young children with fever?

SUMMARY ANSWER

The traffic light system failed to identify a substantial proportion of serious bacterial infections, particularly urinary tract infections, and the addition of urine analysis significantly improved test sensitivity.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The traffic light clinical decision rule was developed by the National Institute for Health and Clinical Excellence (NICE) to guide healthcare professionals in initial assessment of febrile children, but it has not been validated to date.
The addition of urine analysis significantly enhanced the otherwise moderate sensitivity of the traffic light system for detecting serious bacterial infections.

Participants and setting

From 2004 to 2006 the Febrile Evaluation of Children in the Emergency Room (FEVER) cohort study recruited children under 5 years of age who presented consecutively to the emergency department of a tertiary children's hospital with fever and who were not immunocompromised.

Design, size and duration:

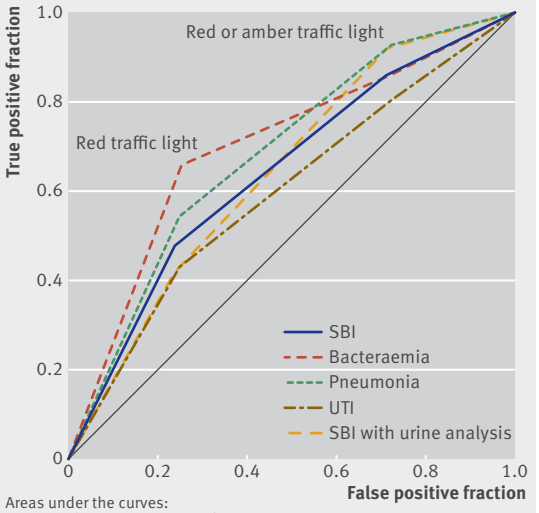
In this retrospective analysis of data from the FEVER study, we matched the symptoms and signs comprising the NICE traffic light system to equivalent clinical items for 15 781 episodes of fever (the system provides a table of clinical features in three colour coded columns denoting the seriousness of febrile illnesses). Each episode was categorised as having low, intermediate, or high probability of serious bacterial infection depending on whether the clinical features matched the green, amber, or red zones of the NICE traffic light system. These results were cross classified with the reference standard for the three most common serious bacterial infections in young children (urinary tract infection, bacteraemia, and pneumonia) separately, and in combination with meningitis, osteomyelitis, and septic arthritis in a composite category of any serious bacterial infection.

Urine analysis was reported in 3653 (23%) of the episodes, and the presence of nitrite or leucocyte esterase was considered as test positive.

Main results and the role of chance

Of the 15 781 eligible febrile illnesses, 1120 (7.1%) were due to one or more serious bacterial infection, with a total of 1166 infections identified. After combination of the intermediate and high risk categories, the NICE traffic light system had a test sensitivity of 85.8% (95% CI 83.6% to 87.7%) and a specificity of 28.5% (27.8% to 29.3%) for the detection of serious bacterial infection (figure). Adding urine analysis to the traffic light system improved the test performance, giving a sensitivity of 92.1% (89.3% to 94.1%), specificity of 22.3% (20.9% to 23.8%), and a relative positive likelihood ratio of 1.10 (1.06 to 1.14).

Receiver operating characteristics curve for performance of the NICE traffic light system, with or without the addition of urine analysis



Areas under the curves:
SBI 0.64 (95% CI 0.62 to 0.66)
Bacteraemia 0.69 (0.63 to 0.76)
Pneumonia 0.68 (0.66 to 0.70)
UTI 0.59 (0.57 to 0.62)
SBI with urine analysis 0.61 (0.58 to 0.63)
SBI=Any serious bacterial infection
UTI=Urinary tract infection

Bias, confounding, and other reasons for caution

In keeping with standard clinical practice, reference standard tests were performed only where clinically indicated, and, despite a two step reference standard process (investigations and clinical follow-up), loss of about 7.1% may have introduced verification bias and an overestimate of the test sensitivity. Although we had data relating to most of the traffic light criteria, some were lacking in our dataset.

Generalisability to other populations

This study was conducted in a paediatric emergency department. We did not assess for generalisability of our findings to other settings such as general practice.

Study funding/potential competing interests

This is a sub-study of FEVER, which was funded by the National Health and Medical Research Council of Australia.