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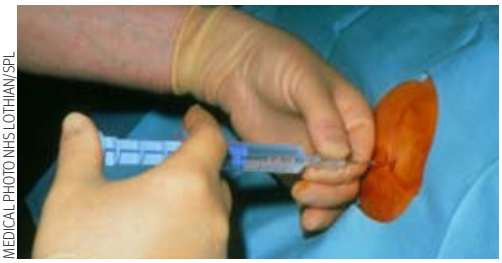
RESEARCH

THIS WEEK'S RESEARCH QUESTIONS

746 Does an epidural block improve cancer-free survival after major abdominal surgery for cancer?

747 How did a reduction in working hours of doctors in postgraduate medical training affect educational and clinical outcome?

748 Are industry funding and other study characteristics associated with reporting of subgroup analyses of trials?



MEDICAL PHOTO NHS LOTHIAN/SPL

Cancer recurrence after surgery with epidural block

Apart from the risk of releasing cancer cells into the circulation, surgical removal of cancer has several immunosuppressive effects that could increase the risk of recurrence. Surgery itself depresses cell mediated immunity; general anaesthesia impairs many immune functions; and opioids used for postoperative pain relief inhibit both cellular and humoral immune function. Regional anaesthesia might avoid such problems by reducing the need for opioids and by suppressing the response to surgical stress. Animal studies support the theory, but the few, small, observational studies in humans have conflicting results.

Paul Myles and colleagues (p 746) now report on their long term follow-up (up to 15 years) of 503 patients who underwent potentially curative abdominal surgery for cancer and were randomised to receiving general anaesthesia with or without epidural block for at least three postoperative days. They found no effect on cancer-free survival. The authors, and the linked editorial by Tsui and Green (p 718), acknowledge the study limitations that could have hidden a real effect—both groups of patients received immunosuppressive general anaesthesia and some opiates, and the heterogeneous nature of the cancers included in the study would have disguised any cancer specific effect. However, the fact that research on this subject reaches back to the 1970s with no conclusive result is not encouraging.

Impact of doctors' shorter working hours on patients' outcomes and postgraduate training

Junior doctors' working hours have been getting shorter over the past 20 years in the United States and Europe. Has this adversely affected patients' outcomes or objectively measured outcomes of doctors' training? Not according to the published evidence, as systematically reviewed by S R Moonesinghe and colleagues (p 747). They analysed the results of 72 studies from the US and UK and found no adverse effects associated with reducing working hours to 80 or fewer a week. The evidence, particularly from the UK, was of relatively low quality, however. So the authors call for bigger and better studies, particularly on the impact of European legislation limiting working hours to 56 or 48 a week. And, given that one of the fundamental principles behind these reforms was to improve patient safety, editorialist Leora I Horwitz from Yale University Medical School asks why they have not benefited patients (p 719).

Industry funding and reporting of subgroup analyses in trials

The CONSORT 2010 statement on reporting parallel group randomised controlled trials asks authors to report "Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory" and warns that "Multiple analyses of the same data create a risk for false positive findings." Authors should resist the temptation to perform many subgroup analyses. Analyses that were prespecified in the trial protocol are much more reliable than those suggested by the data, and therefore authors should report which analyses were prespecified ... Selective reporting of subgroup analyses could lead to bias" (http://bit.ly/ftr5yX).

Several studies have shown associations between industry funding or sponsorship and biases in trial design, conduct, and reporting, but does the same apply to the use of subgroup analysis? Indeed it does, say Xin Sun, from the Chinese Evidence-Based Medicine Center in Chengdu, and colleagues from North America and Europe (p 748). They reviewed 1140 papers reporting randomised controlled trials in 118 core clinical journals in 2007; half from high impact journals and half from lower impact journals. Randomised controlled trials published in high impact journals, with larger sample size, studying non-surgical topics, and with industry funding were associated with more frequent reporting of subgroup analyses if the primary outcome was not statistically significant. It's well worth reading the authors' discussion of their findings in the full paper on bmj.com, where they also note that "Industry funded trials, regardless of the statistical significance of primary outcomes, less often prespecify subgroup hypotheses and less often use the interaction test for analyses of subgroup effects compared with trials that are not funded by industry." This study was funded by the National Natural Science Foundation of China: let's hope it reaches researchers in China, given that so many industry trials are now conducted there.

JOTI/SPL

LATEST RESEARCH: For these and other new research articles see www.bmj.com/research

Group therapy for self harming adolescents J M Green and colleagues found that a targeted group therapy programme was not effective for young people who repeatedly self harmed, although outcomes for the cohort as a whole were better than expected (doi:10.1136/bmj.d682).

Statins for primary prevention of vascular disease J P Greving and colleagues say that in daily practice, statin treatment may not be cost effective for primary prevention of vascular disease in populations at low risk, despite low costs of generic pills. They suggest that improved adherence to statins would enhance cost effectiveness (doi:10.1136/bmj.d1672).

Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial

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EDITORIAL by Tsui and Green

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STUDY QUESTION Does epidural block improve recurrence-free survival of patients having major abdominal surgery for cancer?

SUMMARY ANSWER Use of epidural block in abdominal cancer surgery is not associated with improved cancer-free survival.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Recent observational studies suggest a strong association between use of local anaesthetic (regional) block for cancer surgery and reductions in late recurrence of cancer; these may be misleading because of selection and detection biases. This randomised trial could not identify any reduction in recurrence of cancer or survival when epidural block was used for surgery for abdominal cancer.

Design

This was a long term follow-up of a prospective randomised controlled clinical trial in which patients were randomly assigned to receive general anaesthesia with or without epidural block for at least three postoperative days.

Participants and setting

We included adult patients (n=503) at high risk of recurrence of cancer who had potentially curative surgery for cancer, across 23 hospitals in Australia, New Zealand, and Asia.

Primary outcome

The primary outcome was cancer-free survival up to 15 years after surgery.

BMJ pico: advice to authors

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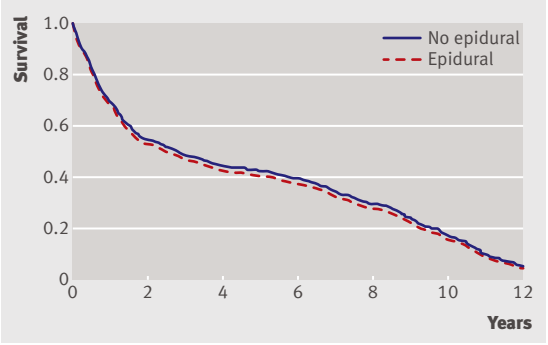
RECURRENCE-FREE SURVIVAL AFTER CANCER SURGERY BY GROUP (LOG RANK P=0.61)



Main results and the role of chance

The median time to recurrence of cancer or death was 2.8 (95% confidence interval 1.7 to 3.8) years in the control group and 2.6 (1.0 to 4.7) years in the epidural group (P=0.61). Recurrence-free survival was similar in both epidural and control groups (hazard ratio 0.95, 95% confidence interval 0.76 to 1.17; P=0.61). We found no evidence of possible benefit in subgroup analyses done for different types of abdominal organ cancers.

Harms

No harms were identified.

Bias, confounding, and other reasons for caution

This was an unblinded study. All patients had a general anaesthetic for their surgery. Around half of the epidural group patients had their epidural removed before three days after surgery. Most patients in the epidural group had at least some morphine perioperatively.

Generalisability to other populations

This was a generally elderly population with comorbidity, at high risk of recurrence of cancer or death and having abdominal surgery. The results may not apply to surgery for other cancers such as breast cancer.

Study funding/potential competing interests

The Australian National Health and Medical Research Council funded the MASTER trial. The cancer follow-up study was funded by the Australian and New Zealand College of Anaesthetists, the Alfred Hospital Research Trust (Melbourne, Australia), and the Department of Outcomes Research at the Cleveland Clinic (OH, USA). PSM is funded by an Australian National Health and Medical Research Council practitioner fellowship.

Trial registration number

Australian New Zealand Clinical Trials Registry ACTRN12607000637448.

Impact of reduction in working hours for doctors in training on postgraduate medical education and patients' outcomes: systematic review

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EDITORIAL by Horwitz

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STUDY QUESTION What is the impact of a reduction in working hours of doctors in postgraduate medical training on objective measures of educational and clinical outcome?

SUMMARY ANSWER Reducing working hours to less than 80 a week has not adversely affected patients' outcomes or postgraduate training in the United States. The impact of reducing hours to less than 56 or 48 a week in the United Kingdom has not yet been sufficiently evaluated in high quality studies.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Legislation limiting duty hours is aimed at improving doctors' working conditions and patient safety; however, concerns have been raised over potential unintended adverse consequences for training standards and patient outcomes. Reductions in working hours do not seem to have had an adverse effect on objective outcomes in patients or postgraduate training.

Selection criteria for studies

Medline, Embase, ISI Web of Science, Google Scholar, ERIC, and SIGLE were searched without language restriction for studies published between 1990 and 2010, and comparing objective outcomes before and after working hours regulations were implemented. Any study design was eligible.

Outcomes

We included any objective outcome measure and excluded surveys of opinion. Educational outcomes included examination scores, caseload in technical specialties, and "training opportunities" (various definitions). Patients' outcomes included morbidity, mortality, patient safety indicators, and length of stay.

Main results and role of chance

We analysed 72 studies: 38 reporting training outcomes, 31 reporting outcomes in patients, and three reporting both. No studies that satisfied our inclusion criteria were identified from outside the US and UK. Most US studies reported no adverse effects on outcomes in patients or postgraduate training. Few UK studies had evaluated the effect of working hours' legislation on patients' outcomes; most found no effect on objective measures of postgraduate training. The literature on training outcomes focuses predominantly on procedural caseload in "technical" specialties, such as surgery and anaesthesia.

Bias, confounding, and other reasons for caution

We could not do a meta-analysis because of the heterogeneity of study design and outcome measures. Several papers, particularly from the UK, were of low methodological quality. Many were small single centre studies and might have been underpowered to detect significant changes. Outcome measures used in studies of postgraduate training might not fully reflect training quality. These observations highlight the requirement for large multicentre evaluations of the effect of working hours' regulations on objective and validated outcome measures.

Study funding/potential competing interests

This study was not commissioned and no project specific funding was received. SRM and JDB were members of the General Medical Council (GMC) EWTD Working Group. SRM works within the UCLH/UCL Joint Comprehensive Biomedical Research Centre, which received funding from the UK Department of Health's National Institute for Health Research Centres funding scheme. Part of this work was conducted while SRM was a National Institute for Academic Anaesthesia (NIAA) Research Fellow, supported by a grant awarded to the NIAA's Health Services Research Centre by the Frances and Augustus Newman Foundation. SRM is a council member of the Royal College of Anaesthetists. JDB is a GMC partner and a member of the Intercollegiate Surgical Curriculum Programme Development Group.

SUMMARY OF LEGISLATION AND RECOMMENDATIONS ON DUTY HOURS FOR DOCTORS' POSTGRADUATE TRAINING IN US AND UK

Variable	Code 405 (New York State, 1989)	ACGME recommendations (US, 2003)	IOM recommendations (US, 2009)	New Deal (UK, 1996)	EWTD (UK, 2004)	EWTD (UK, 2009)
Maximum duty hours/week	80 hours, averaged over 4 weeks	80 hours, averaged over 4 weeks	80 hours, averaged over 4 weeks	56 hours, averaged over 26 weeks	56 hours averaged over 26 weeks	48 hours averaged over 26 weeks
Maximum shift length	24 hours with 3 hour transition period	30 hours (admitting patients up to 24 hours, then 6 additional hours for transitional and educational activities)	30 hours (admitting patients for up to 16 hours, plus 5 hour protected sleep period between 10 pm and 8 am, with remaining hours for transitional and educational activities)	No restriction	13 hours	13 hours
Minimum rest period between shifts	8 hours. At least one 24 hour period off duty/week	10 hours after day shift	10 hours after day shift; 12 hours after night shift; 14 hours after any extended duty period of 30 hours, not returning until 6 am next day	8 hours between shifts, 24 hours every 7 days or 48 hours every 14 days	11 hours between shifts	11 hours between shifts

ACGME=Accreditation Council for Graduate Medical Education, IOM=Institute of Medicine, EWTD=European Working Time Directive.

The influence of study characteristics on reporting of subgroup analyses in randomised controlled trials: systematic review

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STUDY QUESTION

What study characteristics are associated with reporting of subgroup analyses in randomised controlled trials?

SUMMARY ANSWER

Larger sample size, non-surgical interventions, publication in high impact journals, and trials with industry funding that fail to detect a statistically significant effect are more likely to report subgroup analyses.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Our findings that in studies without statistically significant results, industry funding is associated with more subgroup analyses, less prespecification of hypotheses, and less frequent formal tests of interaction are all previously unreported. Caution is needed in interpreting results of subgroup analysis in trials funded by industry with negative findings.

Selection criteria for studies

Randomised controlled trials published in 118 core clinical journals in 2007. Overall, 1140 study reports were randomly sampled, in a 1:1 ratio by high (five general medicine journals with largest number of total citations in 2007) versus lower impact journals.

Primary outcome(s)

Reporting of subgroup analyses.

Main results and role of chance

Subgroup analyses were reported by 207 of 469 (44%) included randomised controlled trials. High impact journals (adjusted odds ratio 2.64, 95% confidence interval 1.62 to 4.33), non-surgical (versus surgical) trials (2.10, 1.26 to 3.50), and larger sample size (3.38, 1.64 to 6.99) were associated with more frequent reporting of subgroup analyses. The strength of association between funding and reporting of subgroups differed in trials with and without statistically significant primary outcomes (interaction P=0.02). In trials without statistically significant results for the primary outcome, industry funded trials were more likely to report subgroup analyses (2.29, 1.30 to 4.72) than non-industry funded trials. This was not true for trials with a statistically significant primary outcome (0.79, 0.46 to 1.36). Industry funded trials were associated with less frequent prespecification of subgroup hypotheses (31.3% *v* 38.0%, adjusted odds ratio 0.49, 0.26 to 0.94), and less use of the interaction test for analyses of subgroup effects (41.4% *v* 49.1%, 0.52, 0.28 to 0.97) than non-industry funded trials.

Bias, confounding, and other reasons for caution

The study sample was limited to trials published in 2007 in core clinical journals. We categorised trials as positive or negative according to the P value threshold of 0.05. This approach to categorising trials might be questioned. Most editors and authors, however, still use such categorisation.

Study funding/potential competing interests

This study is supported by the National Natural Science Foundation of China (project No 70703025). Several of the authors are sponsored by national and academic organisations (see bmj.com).

STUDY CHARACTERISTICS ASSOCIATED WITH REPORTING VERSUS NOT REPORTING OF SUBGROUP ANALYSES

Study characteristics	Odd ratio (95% CI)	P value
High impact *v* lower impact journals	2.64 (1.62 to 4.33)	<0.001
Non-surgical *v* surgical trials	2.10 (1.26 to 3.50)	0.005
Sample size per arm (fourths):		
3-32	1 (reference)	
33-101	1.83 (0.97 to 3.46)	0.062
102-301	3.41 (1.74 to 6.67)	<0.001
≥302	3.38 (1.64 to 6.99)	0.001
No of prespecified primary outcomes	1.08 (0.87 to 1.35)	0.48
Industry funding *v* other:		
When primary outcome was non-significant	2.29 (1.30 to 4.72)	0.005
When primary outcome was significant	0.79 (0.46 to 1.36)	0.91

Estimates were calculated from multivariable logistic regression analysis. The interaction between trial funding with statistical significance of primary outcome and reporting of subgroup analyses was statistically significant (P=0.021).