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BMJ (15 December 2018, Vol. 363, No. 8180)

Due to release of a Christmas Issue there is no new content this week.

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JAMA: Journal of the American Medical Association (18 December 2018, Vol. 320, No. 23)

Association of Maternal First-Trimester Ondansetron Use With Cardiac Malformations and Oral Clefts in Offspring

Krista F. Huybrechts, Sonia Hernández-Díaz, Loreen Straub, et al

JAMA. 2018; 320 (23): 2429-2437.
https://jamanetwork.com/journals/jama/article-abstract/2718793

Abstract

Importance Evidence for the fetal safety of ondansetron, a 5-HT_3 receptor antagonist that is commonly prescribed for nausea and vomiting during pregnancy, is limited and conflicting.

Objective To evaluate the association between ondansetron exposure during pregnancy and risk of congenital malformations.

Design, Setting, and Participants A retrospective cohort study nested in the 2000-2013 nationwide Medicaid Analytic eXtract. The cohort consisted of 1 816 414 pregnancies contributed by 1 502 895 women enrolled in Medicaid from 3 months before the last menstrual period through 1 month or longer after delivery; infants were enrolled in Medicaid for at least 3 months after birth. The final date of follow-up was December 31, 2013. Analyses were conducted between November 1, 2017, and June 30, 2018. Propensity score stratification was used to control for treatment indication and other confounders.

Exposures Ondansetron dispensing during the first trimester, the period of organogenesis.

Main Outcomes and Measures Primary outcomes were cardiac malformations and oral clefts diagnosed during the first 90 days after delivery. Secondary outcomes included congenital malformations overall and subgroups of cardiac malformations and oral clefts.

Results Among 1 816 414 pregnancies (mean age of mothers, 24.3 [5.8] years), 88 467 (4.9%) were exposed to ondansetron during the first trimester. Overall, 14 577 of 1 727 947 unexposed and 835 of 88 467 exposed infants were diagnosed with a cardiac malformation, for an absolute risk of 84.4 (95% CI, 83.0 to 85.7) and 94.4 (95% CI, 88.0 to 100.8) per 10 000 births respectively. The absolute risk of oral clefts was 11.1 per 10 000 births (95% CI, 10.6 to 11.6; 1921 unexposed infants) and was 14.0 per 10 000 births

(95% CI, 11.6 to 16.5; 124 exposed infants). The risk of any congenital malformation was 313.5 per 10 000 births (95% CI, 310.9 to 316.1; 54 174 unexposed infants) and was 370.4 (95% CI, 358.0 to 382.9; 3277 exposed infants). The adjusted relative risk (RR) for cardiac malformations was 0.99 (95% CI, 0.93 to 1.06) and the adjusted risk difference (RD) was −0.8 (95% CI, −7.3 to 5.7 per 10 000 births). For oral clefts, the adjusted RR was 1.24 (95% CI, 1.03 to 1.48) and the RD was 2.7 (95% CI, 0.2 to 5.2 per 10 000 births). The adjusted estimate for congenital malformations overall was an RR of 1.01 (95% CI, 0.98 to 1.05) and an RD of 5.4 (95% CI, −7.3 to 18.2 per 10 000 births).

Conclusions and Relevance Among offspring of mothers enrolled in Medicaid, first-trimester exposure to ondansetron was not associated with cardiac malformations or congenital malformations overall after accounting for measured confounders but was associated with a small increased risk of oral clefts.

Association of Delivery Mode With Pelvic Floor Disorders After Childbirth

Joan L. Blomquist, Alvaro Muñoz, Megan Carroll, et al

JAMA. 2018; 320 (23): 2438-2447.
https://jamanetwork.com/journals/jama/article-abstract/2718794

Abstract

Importance Pelvic floor disorders (eg, urinary incontinence), which affect approximately 25% of women in the United States, are associated with childbirth. However, little is known about the course and progression of pelvic floor disorders over time.

Objective To describe the incidence of pelvic floor disorders after childbirth and identify maternal and obstetrical characteristics associated with patterns of incidence 1 to 2 decades after delivery.

Design, Setting, and Participants Women were recruited from a community hospital for this cohort study 5 to 10 years after their first delivery and followed up annually for up to 9 years. Recruitment was based on mode of delivery; delivery groups were matched for age and years since first delivery. Of 4072 eligible women, 1528 enrolled between October 2008 and December 2013. Annual follow-up continued through April 2017.

Exposures Participants were categorized into the following mode of delivery groups: cesarean birth (cesarean deliveries only), spontaneous vaginal birth (≥1 spontaneous vaginal delivery and no operative vaginal deliveries), or operative vaginal birth (≥1 operative vaginal delivery).

Main Outcomes and Measures Stress urinary incontinence (SUI), overactive bladder (OAB), and anal incontinence (AI), defined using validated threshold scores from the Epidemiology of Prolapse and Incontinence Questionnaire, and pelvic organ prolapse (POP), measured using the Pelvic Organ Prolapse Quantification Examination. Cumulative incidences, by delivery group, were estimated using parametric methods. Hazard ratios, by exposure, were estimated using semiparametric models.

Results Among 1528 women (778 in the cesarean birth group, 565 in the spontaneous vaginal birth group, and 185 in the operative vaginal birth group), the median age at first delivery was 30.6 years, 1092 women (72%) were multiparous at enrollment (2887 total deliveries), and the median age at enrollment was 38.3 years. During a median follow-up of 5.1 years (7804 person-visits), there were 138 cases of SUI, 117 cases of OAB, 168 cases of AI, and 153 cases of POP. For spontaneous vaginal delivery (reference), the 15-year cumulative incidences of pelvic floor disorders after first delivery were as follows: SUI, 34.3% (95% CI, 29.9%-38.6%); OAB, 21.8% (95% CI, 17.8%-25.7%); AI, 30.6% (95% CI, 26.4%-34.9%), and POP, 30.0% (95% CI, 25.1%-34.9%). Compared with spontaneous vaginal delivery, cesarean delivery was associated with significantly lower hazard of SUI

(adjusted hazard ratio [aHR], 0.46 [95% CI, 0.32-0.67]), OAB (aHR, 0.51 [95% CI, 0.34-0.76]), and POP (aHR, 0.28 [95% CI, 0.19-0.42]), while operative vaginal delivery was associated with significantly higher hazard of AI (aHR, 1.75 [95% CI, 1.14-2.68]) and POP (aHR, 1.88 [95% CI, 1.28-2.78]). Stratifying by delivery mode, the hazard ratios for POP, relative to a genital hiatus size less than or equal to 2.5 cm, were 3.0 (95% CI, 1.7-5.3) for a genital hiatus size of 3 cm and 9.0 (95% CI, 5.5-14.8) for a genital hiatus size greater than or equal to 3.5 cm.

Conclusions and Relevance Compared with spontaneous vaginal delivery, cesarean delivery was associated with significantly lower hazard for stress urinary incontinence, overactive bladder, and pelvic organ prolapse, while operative vaginal delivery was associated with significantly higher hazard of anal incontinence and pelvic organ prolapse. A larger genital hiatus was associated with increased risk of pelvic organ prolapse independent of delivery mode.

Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis

Jason W. Busse, Li Wang, Mostafa Kamaleldin, et al.

JAMA. 2018; 320 (23): 2448-2460.
https://jamanetwork.com/journals/jama/article-abstract/2718795

Abstract

Importance Harms and benefits of opioids for chronic noncancer pain remain unclear.

Objective To systematically review randomized clinical trials (RCTs) of opioids for chronic noncancer pain.

Data Sources and Study Selection The databases of CENTRAL, CINAHL, EMBASE, MEDLINE, AMED, and PsycINFO were searched from inception to April 2018 for RCTs of opioids for chronic noncancer pain vs any nonopioid control.

Data Extraction and Synthesis Paired reviewers independently extracted data. The analyses used random-effects models and the Grading of Recommendations Assessment, Development and Evaluation to rate the quality of the evidence.

Main Outcomes and Measures The primary outcomes were pain intensity (score range, 0-10 cm on a visual analog scale for pain; lower is better and the minimally important difference [MID] is 1 cm), physical functioning (score range, 0-100 points on the 36-item Short Form physical component score [SF-36 PCS]; higher is better and the MID is 5 points), and incidence of vomiting.

Results Ninety-six RCTs including 26 169 participants (61% female; median age, 58 years [interquartile range, 51-61 years]) were included. Of the included studies, there were 25 trials of neuropathic pain, 32 trials of nociceptive pain, 33 trials of central sensitization (pain present in the absence of tissue damage), and 6 trials of mixed types of pain. Compared with placebo, opioid use was associated with reduced pain (weighted mean difference [WMD], −0.69 cm [95% CI, −0.82 to −0.56 cm] on a 10-cm visual analog scale for pain; modeled risk difference for achieving the MID, 11.9% [95% CI, 9.7% to 14.1%]), improved physical functioning (WMD, 2.04 points [95% CI, 1.41 to 2.68 points] on the 100-point SF-36 PCS; modeled risk difference for achieving the MID, 8.5% [95% CI, 5.9% to 11.2%]), and increased vomiting (5.9% with opioids vs 2.3% with placebo for trials that excluded patients with adverse events during a run-in period). Low- to moderate-quality evidence suggested similar associations of opioids with improvements in pain and physical functioning compared with nonsteroidal anti-inflammatory drugs (pain: WMD, −0.60 cm [95% CI, −1.54 to 0.34 cm]; physical functioning: WMD, −0.90 points [95% CI, −2.69 to 0.89 points]), tricyclic antidepressants (pain: WMD, −0.13 cm [95% CI, −0.99 to 0.74 cm]; physical functioning: WMD, −5.31 points [95% CI, −13.77 to 3.14 points]), and

anticonvulsants (pain: WMD, −0.90 cm [95% CI, −1.65 to −0.14 cm]; physical functioning: WMD, 0.45 points [95% CI, −5.77 to 6.66 points]).
Conclusions and Relevance In this meta-analysis of RCTs of patients with chronic noncancer pain, evidence from high-quality studies showed that opioid use was associated with statistically significant but small improvements in pain and physical functioning, and increased risk of vomiting compared with placebo. Comparisons of opioids with nonopioid alternatives suggested that the benefit for pain and functioning may be similar, although the evidence was from studies of only low to moderate quality.

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The Lancet (15 December 2018, Vol. 392, No. 10164)

Global patterns of mortality in international migrants: A systematic review and meta-analysis
Robert W Aldridge, Laura B Nellums, Sean Bartlett, et al.
The Lancet: Volume 392, ISSUE 10164, P2553-2566, December 15, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32781-8/fulltext

Summary
Background
258 million people reside outside their country of birth; however, to date no global systematic reviews or meta-analyses of mortality data for these international migrants have been done. We aimed to review and synthesise available mortality data on international migrants.
Methods
In this systematic review and meta-analysis, we searched MEDLINE, Embase, the Cochrane Library, and Google Scholar databases for observational studies, systematic reviews, and randomised controlled trials published between Jan 1, 2001, and March 31, 2017, without language restrictions. We included studies reporting mortality outcomes for international migrants of any age residing outside their country of birth. Studies that recruited participants exclusively from intensive care or high dependency hospital units, with an existing health condition or status, or a particular health exposure were excluded. We also excluded studies limited to maternal or perinatal outcomes. We screened studies using systematic review software and extracted data from published reports. The main outcomes were all-cause and International Classification of Diseases, tenth revision (ICD-10) cause-specific standardised mortality ratios (SMRs) and absolute mortality rates. We calculated summary estimates using random-effects models. This study is registered with PROSPERO, number CRD42017073608.
Findings
Of the 12 480 articles identified by our search, 96 studies were eligible for inclusion. The studies were geographically diverse and included data from all global regions and for 92 countries. 5464 mortality estimates for more than 15·2 million migrants were included, of which 5327 (97%) were from high-income countries, 115 (2%) were from middle-income countries, and 22 (<1%) were from low-income countries. Few studies included mortality estimates for refugees (110 estimates), asylum seekers (144 estimates), or labour migrants (six estimates). The summary estimate of all-cause SMR for international migrants was lower than one when compared with the general population in destination countries (0·70 [95% CI 0·65–0·76]; I^2=99·8%). All-cause SMR was lower in both male migrants (0·72 [0·63–0·81]; I^2=99·8%) and female migrants (0·75 [0·67–0·84]; I^2=99·8%)

compared with the general population. A mortality advantage was evident for refugees (SMR 0·50 [0·46–0·54]; I^2=89·8%), but not for asylum seekers (1·05 [0·89–1·24]; I^2=54·4%), although limited data was available on these groups. SMRs for all causes of death were lower in migrants compared with the general populations in the destination country across all 13 ICD-10 categories analysed, with the exception of infectious diseases and external causes. Heterogeneity was high across the majority of analyses. Point estimates of all-cause age-standardised mortality in migrants ranged from 420 to 874 per 100 000 population.

Interpretation

Our study showed that international migrants have a mortality advantage compared with general populations, and that this advantage persisted across the majority of ICD-10 disease categories. The mortality advantage identified will be representative of international migrants in high-income countries who are studying, working, or have joined family members in these countries. However, our results might not reflect the health outcomes of more marginalised groups in low-income and middle-income countries because little data were available for these groups, highlighting an important gap in existing research. Our results present an opportunity to reframe the public discourse on international migration and health in high-income countries.

Health impacts of parental migration on left-behind children and adolescents: A systematic review and meta-analysis

Gracia Fellmeth, Kelly Rose-Clarke, Chenyue Zhao, et al.

The Lancet: Volume 392, ISSUE 10164, P2567-2582, December 15, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32558-3/fulltext

Summary

Background

Globally, a growing number of children and adolescents are left behind when parents migrate. We investigated the effect of parental migration on the health of left behind-children and adolescents in low-income and middle-income countries (LMICs).

Methods

For this systematic review and meta-analysis we searched MEDLINE, Embase, CINAHL, the Cochrane Library, Web of Science, PsychINFO, Global Index Medicus, Scopus, and Popline from inception to April 27, 2017, without language restrictions, for observational studies investigating the effects of parental migration on nutrition, mental health, unintentional injuries, infectious disease, substance use, unprotected sex, early pregnancy, and abuse in left-behind children (aged 0–19 years) in LMICs. We excluded studies in which less than 50% of participants were aged 0–19 years, the mean or median age of participants was more than 19 years, fewer than 50% of parents had migrated for more than 6 months, or the mean or median duration of migration was less than 6 months. We screened studies using systematic review software and extracted summary estimates from published reports independently. The main outcomes were risk and prevalence of health outcomes, including nutrition (stunting, wasting, underweight, overweight and obesity, low birthweight, and anaemia), mental health (depressive disorder, anxiety disorder, conduct disorders, self-harm, and suicide), unintentional injuries, substance use, abuse, and infectious disease. We calculated pooled risk ratios (RRs) and standardised mean differences (SMDs) using random-effects models. This study is registered with PROSPERO, number CRD42017064871.

Findings

Our search identified 10 284 records, of which 111 studies were included for analysis, including a total of 264 967 children (n=106 167 left-behind children and adolescents; n=158 800 children and adolescents of non-migrant parents). 91 studies were done in China and focused on effects of internal labour migration. Compared with children of non-migrants, left-behind children had increased risk of depression and higher depression scores (RR 1·52 [95% CI 1·27–1·82]; SMD 0·16 [0·10–0·21]), anxiety (RR 1·85 [1·36–2·53]; SMD 0·18 [0·11–0·26]), suicidal ideation (RR 1·70 [1·28–2·26]), conduct disorder (SMD 0·16 [0·04–0·28]), substance use (RR 1·24 [1·00–1·52]), wasting (RR 1·13 [1·02–1·24]) and stunting (RR 1·12 [1·00–1·26]). No differences were identified between left-behind children and children of non-migrants for other nutrition outcomes, unintentional injury, abuse, or diarrhoea. No studies reported outcomes for other infectious diseases, self-harm, unprotected sex, or early pregnancy. Study quality varied across the included studies, with 43% of studies at high or unclear risk of bias across five or more domains.

Interpretation

Parental migration is detrimental to the health of left-behind children and adolescents, with no evidence of any benefit. Policy makers and health-care professionals need to take action to improve the health of these young people.

Eicosapentaenoic acid and aspirin, alone and in combination, for the prevention of colorectal adenomas (seAFOod Polyp Prevention trial): A multicentre, randomised, double-blind, placebo-controlled, 2 × 2 factorial trial

Mark A Hull, Kirsty Sprange, Trish Hepburn, et al

The Lancet: Volume 392, ISSUE 10164, P2583-2594, December 15, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31775-6/fulltext

Summary

Background

The omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA) and aspirin both have proof of concept for colorectal cancer chemoprevention, aligned with an excellent safety profile. Therefore, we aimed to test the efficacy of EPA and aspirin, alone and in combination and compared with a placebo, in individuals with sporadic colorectal neoplasia detected at colonoscopy.

Methods

In a multicentre, randomised, double-blind, placebo-controlled, 2 × 2 factorial trial, patients aged 55–73 years who were identified during colonoscopy as being at high risk in the English Bowel Cancer Screening Programme (BCSP; ≥3 adenomas if at least one was ≥10 mm in diameter or ≥5 adenomas if these were <10 mm in diameter) were recruited from 53 BCSP endoscopy units in England, UK. Patients were randomly allocated (1:1:1:1) using a secure web-based server to receive 2 g EPA-free fatty acid (FFA) per day (either as the FFA or triglyceride), 300 mg aspirin per day, both treatments in combination, or placebo for 12 months using random permuted blocks of randomly varying size, and stratified by BCSP site. Research staff and participants were masked to group assignment. The primary endpoint was the adenoma detection rate (ADR; the proportion of participants with any adenoma) at 1 year surveillance colonoscopy analysed in all participants with observable follow-up data using a so-called at-the-margins approach, adjusted for BCSP site and repeat endoscopy at baseline. The safety population included all participants who received at least one dose of study drug. The trial is registered with the International Standard Randomised Controlled Trials Number registry, number ISRCTN05926847.

Findings

Between Nov 11, 2011, and June 10, 2016, 709 participants were randomly assigned to four treatment groups (176 to placebo, 179 to EPA, 177 to aspirin, and 177 to EPA plus aspirin). Adenoma outcome data were available for 163 (93%) patients in the placebo group, 153 (85%) in the EPA group, 163 (92%) in the aspirin group, and 161 (91%) in the EPA plus aspirin group. The ADR was 61% (100 of 163) in the placebo group, 63% (97 of 153) in the EPA group, 61% (100 of 163) in the aspirin group, and 61% (98 of 161) in the EPA plus aspirin group, with no evidence of any effect for EPA (risk ratio [RR] 0·98, 95% CI 0·87 to 1·12; risk difference −0·9%, −8·8 to 6·9; p=0·81) or aspirin (RR 0·99 (0·87 to 1·12; risk difference −0·6%, −8·5 to 7·2; p=0·88). EPA and aspirin were well tolerated (78 [44%] of 176 had ≥1 adverse event in the placebo group compared with 82 [46%] in the EPA group, 68 [39%] in the aspirin group, and 76 [45%] in the EPA plus aspirin group), although the number of gastrointestinal adverse events was increased in the EPA alone group at 146 events (compared with 85 in the placebo group, 86 in the aspirin group, and 68 in the aspirin plus placebo group). Six upper-gastrointestinal bleeding events were reported across the treatment groups (two in the EPA group, three in the aspirin group, and one in the placebo group).

Interpretation

Neither EPA nor aspirin treatment were associated with a reduction in the proportion of patients with at least one colorectal adenoma. Further research is needed regarding the effect on colorectal adenoma number according to adenoma type and location. Optimal use of EPA and aspirin might need a precision medicine approach to adenoma recurrence.

Analgesic efficacy and safety of morphine in the Procedural Pain in Premature Infants (Poppi) study: Randomised placebo-controlled trial

Caroline Hartley, Fiona Moultrie, Amy Hoskin, et al

The Lancet: Volume 392, ISSUE 10164, P2595-2605, December 15, 2018
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31813-0/fulltext

Summary

Background

Infant pain has immediate and long-term effects but is undertreated because of a paucity of evidence-based analgesics. Although morphine is often used to sedate ventilated infants, its analgesic efficacy is unclear. We aimed to establish whether oral morphine could provide effective and safe analgesia in non-ventilated premature infants for acute procedural pain.

Methods

In this single-centre masked trial, 31 infants at the John Radcliffe Hospital, Oxford, UK, were randomly allocated using a web-based facility with a minimisation algorithm to either 100 μg/kg oral morphine sulphate or placebo 1 h before a clinically required heel lance and retinopathy of prematurity screening examination, on the same occasion. Eligible infants were born prematurely at less than 32 weeks' gestation or with a birthweight lower than 1501 g and had a gestational age of 34–42 weeks at the time of the study. The co-primary outcome measures were the Premature Infant Pain Profile–Revised (PIPP-R) score after retinopathy of prematurity screening and the magnitude of noxious-evoked brain activity after heel lancing. Secondary outcome measures assessed physiological stability and safety. This trial is registered with the European Clinical Trials Database (number 2014-003237-25).

Findings

Between Oct 30, 2016, and Nov 17, 2017, 15 infants were randomly allocated to morphine and 16 to placebo; one infant assigned placebo was withdrawn from the study before

monitoring began. The predefined stopping boundary was crossed, and trial recruitment stopped because of profound respiratory adverse effects of morphine without suggestion of analgesic efficacy. None of the co-primary outcome measures differed significantly between groups. PIPP-R score after retinopathy of prematurity screening was mean 11·1 (SD 3·2) with morphine and 10·5 (3·4) with placebo (mean difference 0·5, 95% CI −2·0 to 3·0; p=0·66). Noxious-evoked brain activity after heel lancing was median 0·99 (IQR 0·40–1·56) with morphine and 0·75 (0·33–1·22) with placebo (median difference 0·25, 95% CI −0·16 to 0·80; p=0·25).

Interpretation

Administration of oral morphine (100 µg/kg) to non-ventilated premature infants has the potential for harm without analgesic efficacy. We do not recommend oral morphine for retinopathy of prematurity screening and strongly advise caution if considering its use for other acute painful procedures in non-ventilated premature infants.

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The New England Journal of Medicine (13 December 2018, Vol. 379, No. 24)

Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation

Jean-François Obadia, David Messika-Zeitoun, Guillaume Leurent, et al. for the MITRA-FR Investigators

N Engl J Med 2018; 379: 2297-2306 December 13, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1805374

Abstract

Background

In patients who have chronic heart failure with reduced left ventricular ejection fraction, severe secondary mitral-valve regurgitation is associated with a poor prognosis. Whether percutaneous mitral-valve repair improves clinical outcomes in this patient population is unknown.

Methods

We randomly assigned patients who had severe secondary mitral regurgitation (defined as an effective regurgitant orifice area of >20 mm2 or a regurgitant volume of >30 ml per beat), a left ventricular ejection fraction between 15 and 40%, and symptomatic heart failure, in a 1:1 ratio, to undergo percutaneous mitral-valve repair in addition to receiving medical therapy (intervention group; 152 patients) or to receive medical therapy alone (control group; 152 patients). The primary efficacy outcome was a composite of death from any cause or unplanned hospitalization for heart failure at 12 months.

Results

At 12 months, the rate of the primary outcome was 54.6% (83 of 152 patients) in the intervention group and 51.3% (78 of 152 patients) in the control group (odds ratio, 1.16; 95% confidence interval [CI], 0.73 to 1.84; P=0.53). The rate of death from any cause was 24.3% (37 of 152 patients) in the intervention group and 22.4% (34 of 152 patients) in the control group (hazard ratio, 1.11; 95% CI, 0.69 to 1.77). The rate of unplanned hospitalization for heart failure was 48.7% (74 of 152 patients) in the intervention group and 47.4% (72 of 152 patients) in the control group (hazard ratio, 1.13; 95% CI, 0.81 to 1.56).

Conclusions

Among patients with severe secondary mitral regurgitation, the rate of death or unplanned hospitalization for heart failure at 1 year did not differ significantly between patients who

underwent percutaneous mitral-valve repair in addition to receiving medical therapy and those who received medical therapy alone.

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

Gregg W. Stone, JoAnn Lindenfeld, William T. Abraham, et al. for the COAPT Investigators

N Engl J Med 2018; 379: 2307-2318 December 13, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1806640

Abstract

Background

Among patients with heart failure who have mitral regurgitation due to left ventricular dysfunction, the prognosis is poor. Transcatheter mitral-valve repair may improve their clinical outcomes.

Methods

At 78 sites in the United States and Canada, we enrolled patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy. Patients were randomly assigned to transcatheter mitral-valve repair plus medical therapy (device group) or medical therapy alone (control group). The primary effectiveness end point was all hospitalizations for heart failure within 24 months of follow-up. The primary safety end point was freedom from device-related complications at 12 months; the rate for this end point was compared with a prespecified objective performance goal of 88.0%.

Results

Of the 614 patients who were enrolled in the trial, 302 were assigned to the device group and 312 to the control group. The annualized rate of all hospitalizations for heart failure within 24 months was 35.8% per patient-year in the device group as compared with 67.9% per patient-year in the control group (hazard ratio, 0.53; 95% confidence interval [CI], 0.40 to 0.70; P<0.001). The rate of freedom from device-related complications at 12 months was 96.6% (lower 95% confidence limit, 94.8%; P<0.001 for comparison with the performance goal). Death from any cause within 24 months occurred in 29.1% of the patients in the device group as compared with 46.1% in the control group (hazard ratio, 0.62; 95% CI, 0.46 to 0.82; P<0.001).

Conclusions

Among patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy, transcatheter mitral-valve repair resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 months of follow-up than medical therapy alone. The rate of freedom from device-related complications exceeded a prespecified safety threshold.

Radical Prostatectomy or Watchful Waiting in Prostate Cancer — 29-Year Follow-up

Anna Bill-Axelson, Lars Holmberg, Hans Garmo, et al.

N Engl J Med 2018; 379: 2319-2329 December 13, 2018
https://www.nejm.org/doi/full/10.1056/NEJMoa1807801

Abstract

Background

Radical prostatectomy reduces mortality among men with clinically detected localized prostate cancer, but evidence from randomized trials with long-term follow-up is sparse.

Methods

We randomly assigned 695 men with localized prostate cancer to watchful waiting or radical prostatectomy from October 1989 through February 1999 and collected follow-up data through 2017. Cumulative incidence and relative risks with 95% confidence intervals for death from any cause, death from prostate cancer, and metastasis were estimated in intention-to-treat and per-protocol analyses, and numbers of years of life gained were estimated. We evaluated the prognostic value of histopathological measures with a Cox proportional-hazards model.

Results

By December 31, 2017, a total of 261 of the 347 men in the radical-prostatectomy group and 292 of the 348 men in the watchful-waiting group had died; 71 deaths in the radical-prostatectomy group and 110 in the watchful-waiting group were due to prostate cancer (relative risk, 0.55; 95% confidence interval [CI], 0.41 to 0.74; P<0.001; absolute difference in risk, 11.7 percentage points; 95% CI, 5.2 to 18.2). The number needed to treat to avert one death from any cause was 8.4. At 23 years, a mean of 2.9 extra years of life were gained with radical prostatectomy. Among the men who underwent radical prostatectomy, extracapsular extension was associated with a risk of death from prostate cancer that was 5 times as high as that among men without extracapsular extension, and a Gleason score higher than 7 was associated with a risk that was 10 times as high as that with a score of 6 or lower (scores range from 2 to 10, with higher scores indicating more aggressive cancer).

Conclusions

Men with clinically detected, localized prostate cancer and a long life expectancy benefited from radical prostatectomy, with a mean of 2.9 years of life gained. A high Gleason score and the presence of extracapsular extension in the radical prostatectomy specimens were highly predictive of death from prostate cancer.

Immune Escape of Relapsed AML Cells after Allogeneic Transplantation

Matthew J. Christopher, Allegra A. Petti, Michael P. Rettig, et al.

N Engl J Med 2018; 379:2330-2341 December 13, 2018
https://www.nejm.org/doi/full/10.1056/N_EJMoa1808777

Abstract

Background

As consolidation therapy for acute myeloid leukemia (AML), allogeneic hematopoietic stem-cell transplantation provides a benefit in part by means of an immune-mediated graft-versus-leukemia effect. We hypothesized that the immune-mediated selective pressure imposed by allogeneic transplantation may cause distinct patterns of tumor evolution in relapsed disease.

Methods

We performed enhanced exome sequencing on paired samples obtained at initial presentation with AML and at relapse from 15 patients who had a relapse after hematopoietic stem-cell transplantation (with transplants from an HLA-matched sibling, HLA-matched unrelated donor, or HLA-mismatched unrelated donor) and from 20 patients who had a relapse after chemotherapy. We performed RNA sequencing and flow cytometry on a subgroup of these samples and on additional samples for validation.

Results

On exome sequencing, the spectrum of gained and lost mutations observed with relapse after transplantation was similar to the spectrum observed with relapse after chemotherapy. Specifically, relapse after transplantation was not associated with the acquisition of previously unknown AML-specific mutations or structural variations in immune-related genes. In contrast, RNA sequencing of samples obtained at relapse after transplantation revealed dysregulation of pathways involved in adaptive and innate immunity, including down-regulation of major histocompatibility complex (MHC) class II genes (HLA-DPA1, HLA-DPB1, HLA-DQB1, and HLA-DRB1) to levels that were 3 to 12 times lower than the levels seen in paired samples obtained at presentation. Flow cytometry and immunohistochemical analysis confirmed decreased expression of MHC class II at relapse in 17 of 34 patients who had a relapse after transplantation. Evidence suggested that interferon-γ treatment could rapidly reverse this phenotype in AML blasts in vitro.

Conclusions

AML relapse after transplantation was not associated with the acquisition of relapse-specific mutations in immune-related genes. However, it was associated with dysregulation of pathways that may influence immune function, including down-regulation of MHC class II genes, which are involved in antigen presentation. These epigenetic changes may be reversible with appropriate therapy.

Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

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Abstract

Background

An earlier analysis in this phase 3 trial showed that durvalumab significantly prolonged progression-free survival, as compared with placebo, among patients with stage III, unresectable non–small-cell lung cancer (NSCLC) who did not have disease progression after concurrent chemoradiotherapy. Here we report the results for the second primary end point of overall survival.

Methods

We randomly assigned patients, in a 2:1 ratio, to receive durvalumab intravenously, at a dose of 10 mg per kilogram of body weight, or matching placebo every 2 weeks for up to 12 months. Randomization occurred 1 to 42 days after the patients had received chemoradiotherapy and was stratified according to age, sex, and smoking history. The primary end points were progression-free survival (as assessed by blinded independent central review) and overall survival. Secondary end points included the time to death or distant metastasis, the time to second progression, and safety.

Results

Of the 713 patients who underwent randomization, 709 received the assigned intervention (473 patients received durvalumab and 236 received placebo). As of March 22, 2018, the median follow-up was 25.2 months. The 24-month overall survival rate was 66.3% (95% confidence interval [CI], 61.7 to 70.4) in the durvalumab group, as compared with 55.6% (95% CI, 48.9 to 61.8) in the placebo group (two-sided P=0.005). Durvalumab significantly prolonged overall survival, as compared with placebo (stratified hazard ratio for death, 0.68; 99.73% CI, 0.47 to 0.997; P=0.0025). Updated analyses regarding progression-free survival were similar to those previously reported, with a median duration of 17.2 months in the durvalumab group and 5.6 months in the placebo group (stratified hazard ratio for

disease progression or death, 0.51; 95% CI, 0.41 to 0.63). The median time to death or distant metastasis was 28.3 months in the durvalumab group and 16.2 months in the placebo group (stratified hazard ratio, 0.53; 95% CI, 0.41 to 0.68). A total of 30.5% of the patients in the durvalumab group and 26.1% of those in the placebo group had grade 3 or 4 adverse events of any cause; 15.4% and 9.8% of the patients, respectively, discontinued the trial regimen because of adverse events.

Conclusions

Durvalumab therapy resulted in significantly longer overall survival than placebo. No new safety signals were identified.

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Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
JAMA: The Journal of the American Medical Association	http://jama.ama-assn.org/
The Lancet	www.thelancet.com
The New England Journal of Medicine	http://content.nejm.org/
The British Medical Journal (BMJ), JAMA and the New England Journal of Medicine (NEJM) can be accessed in full-text through your NHS Athens account. Unfortunately the national subscription to The Lancet has been cancelled.	https://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases or http://www.openathens.net/
If you have not already registered for an NHS Athens Account, please register at: NB: It is recommended that you register on a Trust (NHS) PC for speedy confirmation of your username and password. Once registered, your account can be accessed from any device with online access.	https://openathens.nice.org.uk/

Library News

Christmas Opening Hours

NHS
University Hospitals of Derby and Burton
NHS Foundation Trust

Library and Knowledge Service

Christmas Opening Hours

The Trust Libraries will be staffed at the following times over the Christmas period:-

Opening Times:

Royal Derby Hospital :
Christmas Eve 8am-3pm
27th and 28th December 9am-5pm
31st December 8am-3pm

Queen's Hospital Burton :
Christmas Eve 8.30am-12.30pm
27th and 28th December 10am-2pm
31st December 8.30am-12.30pm

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Everyone in the library would like to wish you all a Merry Christmas and a Happy New Year.

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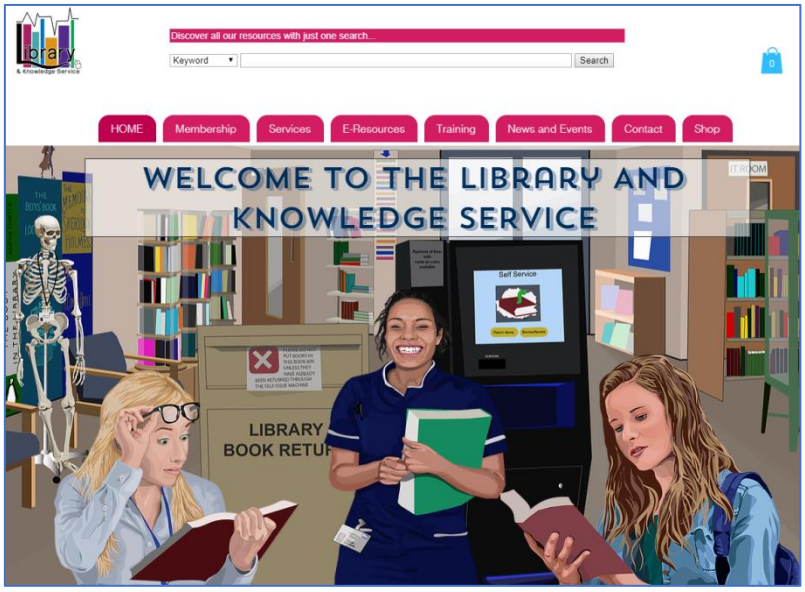

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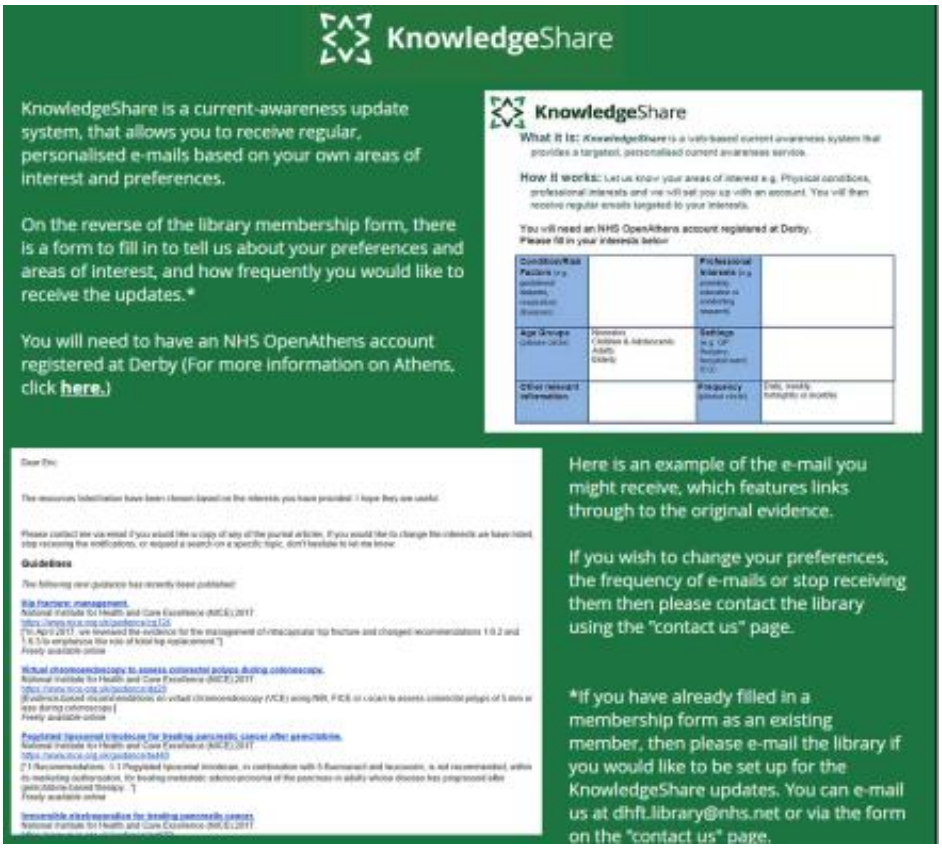

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If you wish to submit a case report, the institutional fellowship code is 4315973. An additional fee needs to be paid by the author if s/he wishes to make their submission open access. Details can be found within the guidance.

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