mechanical ventilation, higher disease severity, and tested later after ICU study discharge.

Suggested by: Bernard De Jonghe, M.D.

The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and healthcare-associated bloodstream infections: Results of a quasi-experimental multicenter trial. Crit Care Med 2009; 37:1858–65

Nearly 20% of patients admitted to ICUs develop a healthcare-associated infection during their stay, many of which are multidrug resistant (*e.g.*, methicillin-resistant *Staphylococcus aureus* [MRSA] and vancomycin-resistant *Enterococcus* [VRE]). The spread of multidrug-resistant organisms within the ICU results in substantial morbidity, mortality, increased length of stay, and increased costs of patient care. This multicenter, before and after, interventional study was completed in six ICUs at four academic centers and performed by the Center for Disease Control and Prevention Epicenters program. The incidence of MRSA and VRE colonization and bloodstream infections were measured during a period of bathing with a routine soap for 6 months and the results were then compared with a 6-month period where all admitted patients received daily bathing with a chlorhexidine-containing solution.

A total of 5,293 patients were admitted during the study period, and 11,333 surveillance cultures were performed. Acquisition of MRSA significantly decreased by 32% (5.04 *vs.* 3.44 cases/1,000 patient days, $P = 0.046$), acquisition of VRE significantly decreased by 50% (4.35 *vs.* 2.19 cases/1,000 patient days, $P = 0.008$), and VRE bacteremia was significantly reduced ($P = 0.02$) after the introduction of daily chlorhexidine bathing. Among patients in the ICU for at least 10 days, fewer patients acquired MRSA in the chlorhexidine group compared with the baseline group (4.37 *vs.* 9.93%). VRE-colonized patients who bathed with chlorhexidine had a lower risk of developing VRE bacteremia (relative rate [RR] 3.35; 95% confidence interval, 1.13–9.87; $P = 0.035$), suggesting that the reductions in the level of colonization led to the observed reductions in blood stream infections.

Interpretation

Bloodstream infections strike as many as one in five patients in hospital ICUs; increased hospital costs occur and mortality may be as great as 25%. Chlorhexidine has excellent antimicrobial activity against MRSA and VRE. Although this was not a randomized controlled trial, and thus has methodological limitations, this intervention may have an important impact on healthcare in ICU patients.

Suggested by: Timothy J. Brennan, Ph.D., M.D.

Racial differences in survival after in-hospital cardiac arrest. JAMA 2009; 302:1195–201

In-hospital cardiac arrest is a guide to assess racial disparities in care and cardiac outcomes, because occurrence is linked to process of care, clinical appropriateness of treatment in eligible patients is standardized, and access or compliance is unlikely to confound the results.

Data from the National Registry of Cardiopulmonary Resuscitation, a large prospective registry of patients with in-hospital cardiac arrest, were used to examine the potential differences in survival in patients with in-hospital cardiac arrest because of ventricular arrhythmia. In this cohort study, 10,011 (18.8% black and 81.2% white) consecutive patients with cardiac arrests were enrolled at 274 hospitals. Survival to hospital discharge, successful resuscitation from initial arrest, and postresuscitation survival were assessed.

Rates of survival to discharge were lower for black patients (25.2%) than for white patients (37.4%; unadjusted RR, 0.73). Racial differences significantly narrowed after adjustment for patient characteristics (adjusted RR, 0.81; $P < 0.001$) and hospital site (adjusted RR, 0.89; $P = 0.002$). Lower rates of survival to discharge for blacks reflected lower rates of both successful resuscitation (55.8 *vs.* 67.4% for whites; unadjusted RR, 0.84) and postresuscitation survival (45.2 *vs.* 55.5% for whites; unadjusted RR, 0.85). Adjustment for the hospital site explained a substantial portion of the racial differences in successful resuscitation (adjusted RR, 0.92; $P < 0.001$) and eliminated the racial differences in postresuscitation survival (adjusted RR, 0.99; $P = 0.68$).

Interpretation

Medical and socioeconomic influence may account for disparities in survival between races. This study provides the background for improving postcardiac arrest survival in minority patients by advancing cardiopulmonary resuscitation performance and improving equipment in specific medical centers.

Suggested by: Jean Mantz, M.D., Ph.D.

Perioperative Medicine

J. Lance Lichtor, M.D., and Joseph F. Antognini, M.D., Editors

Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009; 361:1368–75

Payers and regulators are currently assessing ways to reduce the variability in hospital mortality associated with inpatient surgery. These include incentive plans to increase compliance with evidence-based practices and withholding of payment for preventable complications. In addition, the variation in response to patients with major complications may also contribute to variable rates of death.

Data from 84,730 patients, who had undergone inpatient general and vascular surgery from 2005 to 2007, were collected from the American College of Surgeons National Surgical Quality Improvement Program. Hospitals were ranked according to their risk-adjusted overall rate of death and the incidence of overall and major complications. The rate of death among patients with major complications was also assessed.

Rates of death varied widely across hospitals, from 3.5% (low-mortality hospitals) to 6.9% (high-mortality hospitals, odds ratio, 2.04). Patients at very-high-mortality hospitals were more likely to be nonwhite and smokers. Rates of overall complications (24.6 and 26.9%, respectively) and major complications (18.2 and 16.2%, respectively) were similar despite differences in hospital rate of mortality. Rates of individual complications did not vary significantly across hospital mortality groups (*e.g.*, urinary tract infections, deep venous thromboembosis, or postoperative bleeding). In contrast, mortality in patients with major complications was almost twice as high in hospitals with high overall mortality compared with those with very low overall mortality (21.4 *vs.* 12.5%, $P < 0.001$).

Interpretation

Mortality and morbidity were examined in a large group of surgical patients (84,730) treated at numerous hospitals. Although complication rates were similar among hospitals, death rates varied. These data suggest that failure to timely treat complications may contribute to variability in perioperative mortality.

Suggested by: Joseph F. Antognini, M.D.

Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med 2009; 361:594–604

Although use of heparins, vitamin K antagonists, and mechanical methods to prevent venous thromboembolism after major joint surgery has become the standard practice, subclinical venous thrombosis still develops in 15–40% of patients postsurgery and in 2–4% patients within 3 months of surgery. Furthermore, these agents can be inconvenient. Low-molecular-weight heparins such as enoxaparin predominantly inhibit factor Xa and to some extent thrombin. Apixaban, a specific factor Xa inhibitor, may provide effective thromboprophylaxis with a low risk of bleeding and improved ease of use.

Patients in this double-blinded study undergoing total knee replacement were randomized to receive 2.5 mg of apixaban orally twice daily or 30 mg of enoxaparin subcutaneously every 12 h. Both medications were started 12 to 24 h after surgery and continued for 10 to 14 days. Bilateral venography was then performed. Patients were followed up for 60 days after anticoagulation therapy was stopped.

A total of 3,195 patients underwent randomization (apixaban, n = 1,599; enoxaparin, 1,596) and 908 patients were not eligible for efficacy analysis. The majority of patients (61%) were women. The rate of the primary composite endpoint (asymptomatic and symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, and death from any cause during treatment) was 9.0% with apixaban when compared with 8.8% with enoxaparin (RR, 1.02). Deep-vein thrombosis occurred in 8% of patients in the apixaban and enoxaparin groups. At the 60-day follow-up, symptomatic venous thromboembolism was present in 0.3 and 0.5% of apixaban and enoxaparin patients, respectively. The incidence of major bleeding and clinically relevant nonmajor bleeding was 2.9 and 4.3% with apixaban and enoxaparin, respectively ($P = 0.03$).

Interpretation

Rates of deep-vein thrombosis, pulmonary embolism, or death from any cause were not different in patients who received enoxaparin or apixaban after knee replacement. Apixaban was associated with lower rates of clinically relevant bleeding and it had a similar adverse-event profile.

Suggested by: Lance Lichtor, M.D.

Fluvastatin and perioperative events in patients undergoing vascular surgery. N Engl J Med 2009; 361:980–9

Postoperative cardiac events (*e.g.*, myocardial infarction and death from cardiovascular causes) are common among patients with atherosclerotic vascular disease who undergo noncardiac vascular surgery. Cardiac events occur in 24% of patients in high-risk cohorts. Coronary plaque, thrombus formation, and subsequent vessel occlusion and the inflammatory surgical stress response may contribute to these events.

The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography III (DECREASE III) trial was conducted in adult patients scheduled for noncardiac vascular surgery. Patients who had not been previously treated with a statin were randomly assigned to receive a β-blocker and either 80 mg of extended-release fluvastatin or placebo once daily before undergoing vascular surgery and continued for at least 30 days after surgery. Lipids, interleukin-6, and C-reactive protein levels were measured at the time of randomization and before surgery. The primary endpoint was the occurrence of myocardial ischemia, defined as transient electrocardiographic abnormalities, release of troponin T, or both, within 30 days after surgery. The secondary endpoint was the composite of death from cardiovascular causes and myocardial infarction.

A total of 250 patients were assigned to fluvastatin and 247 to placebo, a median of 37 days before vascular surgery. The majority of patients underwent abdominal aortic surgery (47.5%) or lower-limb arterial surgery (38.6%). Levels

of total cholesterol, low-density lipoprotein cholesterol, interleukin-6, and C-reactive protein were significantly decreased in the fluvastatin group ($P = 0.001$) but were unchanged in the placebo group. Postoperative myocardial ischemia occurred in 10.8% of patients in the fluvastatin group and in 19% of patients in the placebo group (hazard ratio, 0.55; $P = 0.01$). Death from cardiovascular causes or myocardial infarction occurred in 12 patients (4.8%) in the fluvastatin group and in 25 patients (10.1%) in the placebo group (hazard ratio, 0.47; $P = 0.03$).

Interpretation

Perioperative fluvastatin therapy was associated with an improvement in postoperative cardiac outcome. This study supports the use of routine perioperative statins in high-risk patients undergoing vascular surgery.

Suggested by: Lance Lichtor, M.D.

Pain Medicine

Timothy J. Brennan, Ph.D., M.D., Editor

Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron 2009; 63:533–43

Placebo effects are observed throughout randomized clinical trials and across diverse clinical fields. Placebo analgesia causes release of endogenous opioids in dorsolateral prefrontal cortex, rostral anterior cingulate cortex, and periaqueductal gray areas of the brain, and it inhibits pain transmitting regions of the brain such as the thalamus, insula, and dorsal anterior cingulated cortex. The authors hypothesized that placebo analgesia may activate the opioidergic descending pain-control system, perhaps resulting in the inhibition of nociceptive processes at the spinal cord level.

In this randomized, double-blinded study, volunteers received either naloxone (0.15 mg/kg bolus) or saline approximately 15 min before the test phase. Patients were informed that they were being treated with either "lidocaine" or "control" cream and then they received thermal stimulation on days 1 and 2; similar procedures were followed while patients were evaluated using functional magnetic resonance imaging. Naloxone reduced both behavioral and neural placebo effects as well as placebo-induced responses in pain-modulatory cortical structures, such as rostral anterior cingulate cortex. In a brainstem-specific analysis, a similar naloxone modulation of placebo-induced responses in key structures of the descending pain control system, including the hypothalamus, periaqueductal gray, and the rostral ventromedial medulla was observed. Most importantly, naloxone abolished placebo-induced coupling between rostral anterior cingulate cortex and periaqueductal gray, which predicted both neural and behavioral placebo effects as well as activation of the rostral ventromedial medulla.

Interpretation

For placebo analgesia, cortical regions activate the hypothalamus, midbrain periaqueductal gray, and brainstem rostral ventromedial medulla, which signal spinal inhibitory processing of nociceptive information. This may be a pathway used by other endogenous pain modulating systems.

Suggested by: Timothy J. Brennan, Ph.D., M.D.

No evidence for the development of acute tolerance to analgesic, respiratory depressant, and sedative opioid effects in humans. Pain 2009; 142:17–26

Although the association of chronic opioid therapy with the development of pharmacologic tolerance is well accepted, the effects of acute opioid administration are less well defined. Acute tolerance has been demonstrated in animal studies, and human trials examining intraoperative opioid administration have provided mixed results.

In this randomized, double-blinded, placebo-controlled trial, volunteers received a 3-h intravenous infusion delivering two clinically relevant doses of the μ-opioid receptor agonist, remifentanil. The blood remifentanil concentration *versus* opioid effect relationship was determined before and after infusion. Tolerance was inferred if the potency of remifentanil was significantly lower after the infusion. The cold pressor test and models of electrical and heat pain were used to assess opioid analgesia. Pa_{CO_2} and minute ventilation and subjective sedation scores were also measured.

Neither dose of remifentanil produced detectable tolerance to any of the measured opioid effects after a 3-h infusion. Baseline ratings for heat-induced and electrically induced pain were 51 ± 12 and 42 ± 11 mm, and 47 ± 13 and 42 ± 14 mm, 30-min after stopping the infusion, respectively. Baseline and 30-min postinfusion endurance of pain induced by the cold pressor test were 28 ± 8 s and 22 ± 10 s. There were weak but significant associations between blood remifentanil concentration and the magnitude of euphoria and pruritus. No significant association between drug concentration and nausea was detected.

Interpretation

Acute tolerance to potent opioids such as fentanyl and remifentanil is a controversial subject. Concerns arise about the intraoperative use of high doses of these drugs because acute tolerance may blunt opioid analgesia for postoperative pain. The authors could not detect acute tolerance to 3-h remifentanil infusions equivalent to approximately 0.13 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Acute tolerance to remifentanil in the dosages used in this study is not evident.

Suggested by: Timothy J. Brennan, Ph.D., M.D.