TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Intensive care update: Seven studies that should change your practice

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ABSTRACT

Seven recent studies in intensive care found that:

- The need for intravenous sedation should continually be reassessed
- Low-dose dopamine does not offer significant renal protection
- Higher doses of continuous venovenous hemofiltration may improve survival
- Subclavian central venous catheterization is associated with fewer complications than the femoral route
- We have little evidence to support the use of ranitidine and sucralfate as prophylaxis for stress ulcers
- Many young patients with suspected bacterial meningitis can undergo lumbar puncture without a CT scan if they have no abnormalities on a quick history and physical examination
- Intensive insulin therapy to control blood glucose lowers the mortality rate.

SEVEN RECENT STUDIES are changing how we practice in the intensive care unit (ICU). Some of these studies lay to rest widely used but ineffective therapies; others should challenge us to establish new standards of care. And the findings should humble us when we think about how little scientific evidence we have to support much of what we do. Indeed, we often practice empirically, based on tradition and what our mentors did.

KEEP REASSESSING THE NEED FOR CONTINUOUS IV SEDATION

KRESS JP, POHLMAN AS, O'CONNOR MF, HALL JB. DAILY INTERRUPTION OF SEDATIVE INFUSIONS IN CRITICALLY ILL PATIENTS UNDERGOING MECHANICAL VENTILATION. N ENGL J MED 2000; 342:1471–1477.

The use of sedatives and analgesics to decrease discomfort and pain is very common for patients receiving mechanical ventilation.[1] In a study at The Cleveland Clinic,[2] 85% of such patients received intravenous (IV) sedation.

However, the use of IV sedation by continuous infusion may be associated with longer intubation and longer stays in the ICU and in the hospital.[3] Could IV sedation be decreased, and would this decrease the length of ventilation and length of stay?

The study. Kress et al[4] performed a randomized, controlled trial in patients receiving mechanical ventilation in one medical ICU. Sixty patients were enrolled in the control group and 68 in the intervention group. The sedatives were propofol and midazolam by continuous infusion; the analgesic used was morphine.

In the intervention group, an investigator interrupted the sedative infusion every day and waited until the patient either woke up and could follow instructions or became uncomfortable or agitated, in which case the infusion was resumed. If the sedative was resumed, half of the previous dose was given and adjusted according to need. The control group had the sedation interrupted only at the discretion of the medical ICU team.

Findings. Interrupting the infusion was good. Patients in the intervention group had a shorter duration of mechanical ventilation (4.9 days vs 7.3 days, $P = .004$) and a shorter median length of stay in the ICU (6.4 days vs

New findings that should challenge our practice

Higher doses of continuous hemofiltration are better than lower doses

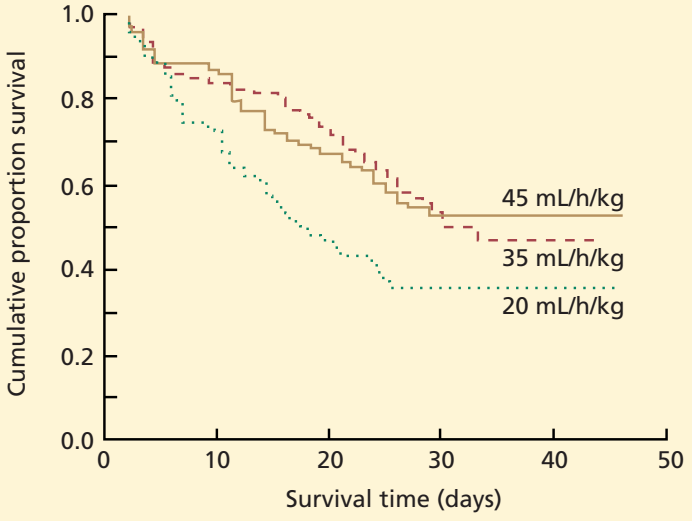

FIGURE 1. Kaplan-Meier estimation of survival rates in 425 patients with acute renal failure in the intensive care unit randomized to receive one of three different doses of continuous venovenous hemofiltration.

FROM RONCO C, BELLOMO R, HOMEL P, ET AL. EFFECTS OF DIFFERENT DOSES IN CONTINUOUS VENO-VENOUS HAEMOFILTRATION ON OUTCOMES OF ACUTE RENAL FAILURE: A PROSPECTIVE RANDOMISED TRIAL. LANCET 2000; 356:26–30.

9.9 days, $P = .02$). They also required less diagnostic testing to assess mental status.

Comments. The message of this paper is to reduce the amount of analgesics and sedatives given to patients in the ICU. It reminds us of the need to reassess practices of sedation and how we measure "adequate" sedation.

LOW-DOSE DOPAMINE DOES NOT PROTECT THE KIDNEYS

AUSTRALIAN AND NEW ZEALAND INTENSIVE CARE SOCIETY (ANZICS) CLINICAL TRIALS GROUP. LOW-DOSE DOPAMINE IN PATIENTS WITH EARLY RENAL DYSFUNCTION: A PLACEBO-CONTROLLED RANDOMISED TRIAL. LANCET 2000; 356:2139–2143.

Acute renal failure is common in the critically ill, and the mortality rate in critically ill patients with acute renal failure remains very high. Dopamine in low doses (0.5 to 2.0 µg/kg/minute) is commonly used in the ICU to prevent acute renal failure by increasing renal blood flow, even though there is no evidence that it is effective.

The study. In a multicenter, randomized, double-blind trial in Australia and New Zealand,[5] 324 ICU patients at risk of acute renal failure (ie, with a serum creatinine concentration > 1.7 mg/dL, a rise in serum creatinine concentration > 0.9 mg/dL, or urine output < 0.5 mL/kg/hour, plus signs of the systemic inflammatory response syndrome [SIRS]) received either low-dose dopamine (2 µg/kg/minute IV) or placebo.

Findings. Dopamine didn't do anything. The serum creatinine and urea concentrations increased similarly in both groups. Similar numbers of patients needed renal replacement therapy in both groups. Urine output increased similarly in both groups, perhaps because many patients received loop diuretics. There was no difference in other secondary outcomes, such as duration of mechanical ventilation, length of stay in the ICU and hospital, cardiac arrhythmias, or survival.

Comments. This large randomized study supports the view that low-dose dopamine does not offer significant renal protection. It is unclear if dopamine is of any use if started before there is any evidence of renal dysfunction; however, the current evidence does not support it.

CONTINUOUS HEMOFILTRATION: MORE IS BETTER, UP TO A POINT

RONCO C, BELLOMO R, HOMEL P, ET AL. EFFECTS OF DIFFERENT DOSES IN CONTINUOUS VENO-VENOUS HAEMOFILTRATION ON OUTCOMES OF ACUTE RENAL FAILURE: A PROSPECTIVE RANDOMISED TRIAL. LANCET 2000; 356:26–30.

Acute renal failure in the ICU is often treated with continuous hemofiltration, even though no clear advantage over intermittent hemodialysis has ever been demonstrated. Furthermore, there is no consensus on the adequate treatment dose or the impact of the dose on outcome.

The study. Ronco et al,[6] in a study in one ICU in Italy, randomized 425 patients with acute renal failure to receive hemofiltration at 20, 35, or 45 mL/h/kg. The reason for the renal failure was mainly postsurgical. All patients reached at least 85% of the prescribed dose of ultrafiltration.

Findings. The dose made a difference. The survival rate 15 days after treatment was stopped was 41% for the patients receiving 20 mL/h/kg, compared with 57% and 58% in the

groups receiving 35 and 45 mL/h/kg, respectively. The median length of survival for the group receiving 20 mL/h/kg was 19 days, compared with 33 days for the group receiving 35 mL/h/kg (P = .0007) and 46 days for the group receiving 45 mL/h/kg (P = .0013; **FIGURE 1**).

The difference in survival between the two groups receiving high-dose ultrafiltration (35 and 45 mL/h/kg) was not statistically significant, however.

The frequency of complications was low and did not differ among the three groups. More than 90% of the patients who survived had full recovery of renal function 15 days after the continuous hemofiltration was stopped.

Comments. This study suggests that the hemofiltration dose may have an impact on survival in patients with acute renal failure admitted to the ICU. The authors suggested that treatment is best started early.

SUBCLAVIAN CATHETERIZATION IS BETTER THAN FEMORAL

MERRER J, DE JONGHE B, GOLLIOT F, ET AL. COMPLICATIONS OF FEMORAL AND SUBCLAVIAN VENOUS CATHETERIZATION IN CRITICALLY ILL PATIENTS. JAMA 2001; 286:700–707.

Central venous catheters are essential for many patients, especially in the ICU. However, the incidence of mechanical, infectious, and thrombotic complications is high.

Are any routes of insertion less prone to complications than others? In a recent meta-analysis,[7] Ruesch et al analyzed six trials and found that insertion of catheters in the internal jugular vein was associated with more arterial punctures than was the subclavian route, but they found no differences in the rates of pneumothorax between the two routes. But what about the femoral route?

The study. Merrer et al[8] did a concealed, randomized controlled trial in eight ICUs in France, comparing femoral vs subclavian catheterization for the rates and risk factors associated with mechanical, infectious, and thrombotic complications in 289 adults receiving their first central line.

Findings. Subclavian was better. Femoral catheterization was associated with a higher rate of infectious and thrombotic complications, although the rates of overall and major mechanical complications were similar between the two groups.

The rate of mechanical complications was high for both groups, nearly 18%. The most common complications were punctures of arteries, bleeding, and hematomas. The factors associated with mechanical complications were insertion at night, duration of catheter insertion (any additional minute), the duration of catheter placement, and catheter insertion at two of the participating centers.

The significant factor associated with an infectious complication was insertion at the femoral site (hazard rate 4.83, 95% CI 1.96–11.93; P < .001), whereas the use of antibiotic infusion via the catheter decreased the rate of infection.

The rate of catheter-related thrombosis was 21% with femoral catheters, compared with 1.9% with subclavian catheters (P < .001). Major thrombosis occurred in 6% of the patients in the femoral group and none in the subclavian catheter group (P = .01).

Most important: the estimated absolute risk reduction associated with subclavian catheterization rather than femoral catheterization was 33% (95% CI 23% to 43%) for all complications and 6% for major complications. Three patients need to receive subclavian rather than femoral catheters to prevent 1 complication of catheterization, and 16 patients to prevent 1 major complication.

Comments. It seems that the best route is subclavian, because it is associated with fewer complications than the internal jugular and femoral routes.

More patients had complications with femoral vs subclavian catheterization

NO EVIDENCE FOR H_2 BLOCKERS IN PREVENTING STRESS ULCERS

MESSORI A, TRIPPOLI S, VAIANI M, GORINI M, CORRADO A. BLEEDING AND PNEUMONIA IN INTENSIVE CARE PATIENTS GIVEN RANITIDINE AND SUCRALFATE FOR PREVENTION OF STRESS ULCER: META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS. BMJ 2000; 321:1103–1106.

Gastrointestinal bleeding, a common manifestation of gastric mucosal injury, occurs in approximately 20% of ICU patients who do not receive prophylactic therapy; however, only in 2% to 6% of patients is the bleeding serious enough to cause a drop in the blood pressure or to require blood transfusion.

Histamine$_2$ (H_2) receptor blockers (usually ranitidine) and sucralfate are commonly

used to prevent gastrointestinal bleeding in patients admitted to the ICU. However, the evidence for their benefit is not strong, and these drugs might contribute to nosocomial pneumonia by reducing gastric acidity, making the stomach more hospitable to bacteria.

The study. Messori et al[9] did a meta-analysis of studies done between 1966 and June 20, 2000, to assess the effectiveness of ranitidine and sucralfate in ICU patients and to evaluate the infectious complications of the use of these two drugs.

Findings. No significant benefit of ranitidine was found when compared with placebo. Only one report compared sucralfate vs placebo. When ranitidine or sucralfate was compared with placebo to assess the rate of pneumonia, no significant difference was found. However, when the incidence of pneumonia was assessed in a fifth meta-analysis (ranitidine vs sucralfate) that included eight randomized trials, a significantly increased risk of pneumonia with ranitidine was found (summary odds ratio 1.51, 95% CI 1.00 to 2.29, $P = .05$).

The authors concluded that ranitidine is ineffective in preventing gastrointestinal bleeding and might increase the risk of pneumonia, and that studies with sucralfate were inconclusive. However, the conclusions were based on small numbers of patients and are not firm.

Comments. Current recommendations on prophylaxis for stress ulcers should be revised. We need more studies that allow us to calculate with accuracy the risk of bleeding in various populations and the risk of pneumonia with various agents, to provide cost-effective stress ulcer prophylaxis.

CT NOT ALWAYS NEEDED BEFORE LUMBAR PUNCTURE

HASBUN R, ABRAHAMS J, JEKEL J, QUAGLIARELLO VJ. COMPUTED TOMOGRAPHY OF THE HEAD BEFORE LUMBAR PUNCTURE IN ADULTS WITH SUSPECTED MENINGITIS. N ENGL J MED 2001; 345:1727–1733.

Getting a CT scan took more than 2 hours

Bacterial meningitis is a medical emergency, and the only way to make the diagnosis is by performing a lumbar puncture. Some clinicians routinely order a computed tomographic (CT) scan before doing a lumbar puncture to avoid brain herniation, but this introduces a delay in a situation in which time is critical. Could some patients forego a CT scan on the basis of a quick history and physical examination?

The study. Hasbun et al[10] prospectively examined 301 patients about to undergo lumbar puncture because of suspected meningitis, of whom 235 (78%) had a CT scan first. Eighty (27%) of the patients subsequently proved to have meningitis, 6% had a pathogen identified on the basis of cerebrospinal fluid analysis, and 7% had a positive blood culture.

Findings. The time from admission to the emergency room to lumbar puncture was longer in the patients who underwent CT scanning (5.3 hours vs 3 hours, $P < .001$). If the patients were younger than 60 years and had no abnormality on the history and physical examination, in 97% of cases the CT scan of the head was normal. If an abnormality was present at baseline, the CT scan was normal in 62%.

The baseline factors associated with abnormal CT scans were:

- Age greater than 60 years
- Immunocompromised status
- History of central nervous system disease
- History of seizure within a week of presentation
- An abnormal neurologic finding.

Only one patient with a normal examination had a mass effect on lumbar puncture, vs 10 patients with an abnormal baseline characteristic.

The investigators estimated that a quick screening such as this could decrease the need for CT scans by at least 41% in patients with suspected meningitis.

Comments. Young patients with no baseline abnormality do not need a CT scan before lumbar puncture.

INTENSIVE INSULIN THERAPY IS BENEFICIAL IN THE ICU

VAN DEN BERGHE G, WOUTERS P, WEEKERS F, ET AL. INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS. N ENGL J MED 2001; 345:1359–1367.

Many ICU patients develop hyperglycemia and insulin resistance, even if they did not have diabetes before. Would insulin therapy to normalize blood glucose levels decrease the mortality rate?

The study. Van den Berghe et al[11] randomly assigned 1,548 patients admitted to a

surgical ICU to receive either intensive IV insulin therapy to keep the blood glucose level between 80 and 110 mg/dL or conventional care, with IV insulin only if the blood glucose level rose above 215 mg/dL and a goal range of 180 to 200 mg/dL.

Findings. Intensive insulin therapy reduced mortality. The mortality rate in the ICU was 4.6% with intensive insulin therapy vs 8.0% with conventional therapy ($P < .04$; **FIGURE 2**). In patients who remained in the ICU for more than 5 days, the mortality rate was 10.6% with intensive therapy vs 20.2% with conventional therapy ($P = .005$). Intensive insulin therapy also reduced in-hospital mortality.

Furthermore, the patients treated with the intensive insulin regimen had fewer episodes of sepsis, shorter length of stay in the ICU, less need for prolonged mechanical ventilation and renal replacement therapy, and a lower incidence of polyneuropathy, a common complication in ICU patients.

Comments. A major limitation of the study is that the population was mainly surgical patients. However, I think the study has significant implications and suggests that adequate control of blood glucose is associated with good outcomes.

Intensive insulin therapy lowers mortality in intensive care patients

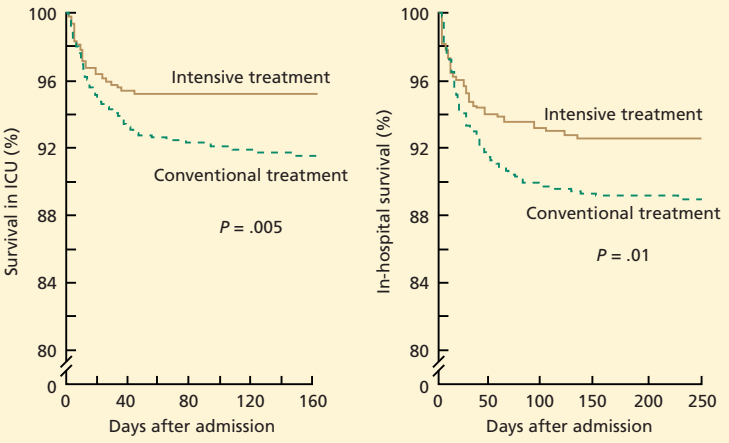

FIGURE 2. Kaplan-Meier curves showing cumulative survival in the intensive care unit (left) and in the hospital (right) of patients who received intensive insulin treatment or conventional treatment in the intensive care unit.

FROM VAN DEN BERGHE G, WOUTERS P, WEEKERS F, ET AL. INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS. N ENGL J MED 2001; 345:1359–1367.

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