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Which Vasopressor Is Best in Patients with Shock?

ABSTRACT & COMMENTARY

By Andrew M. Luks, MD

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Dr. Luks reports no financial relationship to this field of study.

Synopsis: *This randomized, multicenter trial showed no differences in 28-day mortality in patients with shock who received either norepinephrine or dopamine, but did reveal a higher incidence of arrhythmia in the dopamine-treated group.*

Source: De Backer D, et al; SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010;362:779-789.

Consensus guidelines recommend the use of either dopamine or norepinephrine as first-line therapy for patients with shock, but recent observational evidence suggests norepinephrine may be associated with better outcomes. De Backer and colleagues sought to confirm these results in a prospective manner by evaluating whether one of these agents was associated with a lower mortality rate in patients with shock.

They conducted a double-blind, randomized trial at 8 centers in 3 countries in which they enrolled patients at least 18 years of age who required a vasopressor for management of shock, defined as mean arterial pressure (MAP) < 70 mm Hg or SBP < 100 mm Hg despite receiving fluids, or having a central venous pressure (CVP) > 12 with signs of tissue hypoperfusion. Patients with all forms of shock, including septic, cardiogenic, and hypovolemic, were included. Patients were excluded if they had already received a vasopressor for > 4 hours during the current shock episode or had a serious arrhythmia (e.g., rapid atrial fibrillation).

Enrolled patients were randomized to receive either dopamine or norepinephrine. Dopamine was titrated in increments of 2 g/kg/min

up to a maximum of 20 g/kg/min, for a target blood pressure determined by the treating physician, while norepinephrine was titrated in increments of 0.02 g/kg/min up to a maximum dose of 0.19 g/kg/min. Patients who remained hypotensive on the maximum dose of either agent were then started on open-label norepinephrine, while any patients on vasopressors at baseline were changed over to the study drug. Patients could still receive either hydrocortisone or recombinant activated protein C as part of sepsis management. The primary study endpoint was the rate of death at 28 days, while secondary endpoints included rates of death in the ICU, hospital, and at 6 and 12 months, ICU length of stay, number of days without organ support (e.g., mechanical ventilation, renal replacement therapy), time to reach MAP > 65 mm Hg, and use of dobutamine and other inotropic agents. The incidence of adverse events including arrhythmias, myocardial necrosis, skin necrosis, distal ischemia, or secondary infections, was also recorded.

A total of 1679 patients were enrolled in the study including 858 in the dopamine group and 821 in the norepinephrine group. The groups were well matched in terms of major baseline characteristics including the use of hydrocortisone or activated protein C, but there were small differences in baseline physiologic variables such as the heart rate, $PaCO_2$, and PaO_2/FiO_2 (P/F ratio). The majority (62%) of patients had septic shock, while 16.7% had cardiogenic shock and 15.7% had hypovolemic shock. With regard to the primary endpoint, there were no differences in the rate of death at 28 days between the dopamine and norepinephrine groups (52.5% vs 48.5%; $P = 0.10$) and the trial was subsequently stopped due to a lack of evidence of benefit for one agent over the other. Of note, however, was the fact that the mortality rate in patients with cardiogenic shock was higher in those treated with dopamine than those treated with norepinephrine. ICU and hospital mortality and death rates at 6 and 12 months also showed no difference between the two groups. The incidence of adverse events was similar between the two groups except more patients in the dopamine group had arrhythmias, the most common of which was atrial fibrillation.

COMMENTARY

Vasopressors are such commonly used medications in the ICU that it would be nice to have some data as to which agent is more effective for resolving hypotension and improving outcomes in critically ill patients. It is not clear, however, that this trial provides an adequate answer to that question, as there were some methodological issues that warrant concern. For example, patients received fairly limited amount of intravenous fluids before the transition to vasopressors and restrictions were placed on the doses of the vasopressors in an attempt to achieve "equipotent" doses despite the lack of data supporting such a practice.[1]

The biggest problem with the trial by De Backer and colleagues, however, is that they included patients with all forms of shock and did not restrict their study, for example, to patients with septic shock. It was particularly surprising that they included patients with hypovolemic shock, as the primary treatments for that problem are usually to stop any bleeding and restore intravascular volume with aggressive fluid administration. Given differences in the underlying pathophysiology and hemodynamic issues between the different forms of shock, the management of fluids and other medications in the different patient groups would be expected to vary significantly and perhaps make it difficult to tease out differences that one could attribute to one of the particular vasopressors. When one considers variations in physician practices not just between institutions but also between countries, it is not hard to see how many other factors may have been affecting outcomes beyond the choice of vasopressor.

Despite this issue, there are several interesting items that emerge from this study. The first pertains to the safety of using norepinephrine in the ICU. Many of us likely remember the days of reluctance to use that medication out of concern we might have been doing harm to our patients. The phrase "Levophed … Leave 'em dead" was a not uncommon refrain early in my training before the institution made a broader move toward using that vasopressor and physicians became more comfortable with its application.

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This study and another recent study comparing vasopressin and norepinephrine[2] provide reasonable evidence that such concerns are unwarranted and the medication is not associated with more severe adverse events when compared to dopamine.

The second item of note is the observed differences in mortality in the subgroup of patients with cardiogenic shock. From a theoretical point of view, one would expect a vasopressor with significant alpha-1 adrenergic activity to be problematic in patients with cardiomyopathy as the increase in afterload would impair left ventricular outflow. Dopamine has typically been favored in such situations because of its more prominent inotropic effects. The data from this study suggest, however, that the theoretical rationale may not hold in practice and perhaps give clinicians a little more leeway in their use of vasopressors in these patients, although further research is warranted to confirm this subgroup analysis finding before we make a wholesale change in practice. The fact that norepinephrine was associated with less arrhythmia than dopamine would be another advantage in this patient group.

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Reducing Pain on Chest Tube Removal

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In this study in non-intubated post-cardiac surgery patients, a single 0.5 µg/kg intravenous bolus of remifentanil greatly reduced the pain associated with chest drain removal compared to placebo, without the respiratory depression observed with a dose of 1.0 µg/kg.*

Source: Casey E, et al. Bolus remifentanil for chest drain removal in ICU. *Intensive Care Med* 2010 Mar 18; Epub ahead of print.

Casey and colleagues compared the effects on pain, level of consciousness, and vital signs of 2 different doses of remifentanil and placebo for removal of chest drains after cardiac surgery in 60 patients. The patients (mean age, 64 years; 77% men) had undergone coronary artery bypass grafting (40 patients) or valve surgery (20 patients), had been extubated, were hemodynamically stable, and were undergoing routine chest tube removal in the ICU or high-dependency unit on the 2nd or 3rd postoperative day. In double-blind fashion, they were randomized to receive a single dose of intravenous remifentanil (either 1.0 or 0.5 µg/kg) or saline placebo over 1 minute, and then all chest drains (3 in 38 patients, 2 in 22 patients) were removed simultaneously 2 minutes later. All patients had been receiving routine analgesia with morphine, diclofenac, and acetaminophen, with the last doses 2-5 hours (mean, 4 hours) prior to tube removal. Just prior to study drug infusion, again at the time of tube removal, and at 2-minute intervals for the next 10 minutes, the patients indicated their level of pain via a 10-cm visual analog scale, with 0 being "no pain" and 10 "severe pain."

There were no differences in the patients' level of sedation by Ramsay sedation score in the 3 study groups. Patients receiving placebo rated the pain on chest drain removal as 5 (range, 3-6), as compared to those receiving remifentanil 0.5 µg/kg (1; range 0-2) and 1.0 µg/kg (0; range 0-2); $P = 0.001$. Heart rate was significantly reduced following the higher remifentanil dose but was not different between 0.5 µg/kg and placebo. Both remifentanil doses significantly reduced blood pressure and respiratory rate, but not to clinically worrisome levels. The higher dose was followed by a significant decrease in saturation by pulse oximetry (mean, 94% vs 97% with placebo; $P = 0.049$), but there was no change with the 0.5 µg/kg dose. However, two patients became apneic and unresponsive following the 1.0 µg/kg dose, and required several minutes of bag-mask ventilation. No clinically important adverse effects were observed with the lower remifentanil dose. The authors conclude that a remifentanil bolus of 0.5 µg/kg is safe and effective for chest drain removal after heart surgery in the ICU.

COMMENTARY

Many patients who have had cardiac surgery say that removal of the chest drains was the single most painful, distressing part of the experience. This study demonstrates that a single, moderate intravenous dose of the potent synthetic µ-opioid receptor agonist remifentanil substantially reduces this pain, and safely so within the limits of the study's size (20 patients in each group). However, the authors demonstrated that the larger 1.0 µg/kg dose was sufficient to cause apnea in 10% of the patients who received it, and although it was not observed following the 0.5 µg/kg dose (which was basically just as effective in preventing pain), the possibility of this adverse effect occurring cannot be excluded. The authors included only patients in an intensive care environment, and rightly caution against extending this therapy into less intensively staffed areas of the hospital.

Dead Space Fraction as a Prognosticator in ARDS

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In this study of 80 patients with ARDS, an elevated dead space fraction in the first 3 days of lung injury, and also later in the illness at 8-10 days, was associated with increased mortality.*

Source: Raurich JM, et al. Prognostic value of the pulmonary dead-space fraction during the early and intermediate phases of acute respiratory distress syndrome. *Respir Care* 2010;55:282-287.

Raurich and colleagues studied 80 patients with acute respiratory distress syndrome (ARDS) to determine whether the alveolar dead-space fraction (VD/VT, the proportion of each breath that does not participate in gas exchange) was a predictor of ultimate survival. The patients were ages 18 years or older, acutely ill in the investigators' ICU, and met the current international diagnostic criteria for ARDS.[1] Patients with obstructive lung diseases, pulmonary vascular disease, and other conditions that might affect VD/VT were excluded. Using the traditional Enghoff modification of the Bohr equation [$VD/VT = (PaCO_2 - PECO_2)/PaCO_2$] and measuring $PECO_2$ directly from expired air collected in a Douglas bag, the authors determined VD/VT within 3 days of the onset of ARDS, and once again on days 8-10 in patients who remained mechanically ventilated. They then correlated the findings with clinical outcomes.

At both time periods after onset of ARDS, VD/VT correlated with mortality. In the first 3 days its value was 0.53 ± 0.11 among patients who survived, as compared to 0.64 ± 0.09 among patients who died ($P < 0.001$). In the intermediate phase of ARDS (on day 8-10) the corresponding numbers for VD/VT were 0.50 ± 0.10 vs 0.62 ± 0.09 ($P < 0.001$). For every dead-space fraction increase of 0.05 the odds of death increased by 59% in the early phase and by 186% in the intermediate phase, with both results statistically significant.

COMMENTARY

The alveolar dead-space fraction, the ratio of physiologic dead space to tidal volume (VD/VT), is a measure of the efficiency of ventilation. Depending on the delivered tidal volume, it is typically about 0.3 or 0.4 in supine ventilated patients with normal lungs, and is markedly elevated in conditions such as severe chronic obstructive pulmonary disease and pulmonary thromboembolism. Several methods are currently available for determining VD/VT in ventilated patients, and its assessment is useful in the differential diagnosis of patients who are unable to be weaned because of a persistently high minute ventilation.

As reviewed by Kallet and Siobal in the editorial accompanying this article,[2] previous studies have shown that high dead-space fractions correlate with worse outcomes in patients with ARDS. The present study corroborates the previous findings of others that a higher alveolar dead-space fraction in early and intermediate phases of ARDS is associated with a greater risk of death.

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Daily Reminders and Earlier Removal of Central Venous and Urinary Catheters

ABSTRACT & COMMENTARY

By David J. Pierson, MD, Editor

Synopsis: *In this before-after study in a surgical ICU, addition to the daily physician worksheet of a red box requiring the checking of "yes" or "no" to continued need for central venous and urinary catheters was associated with a significant reduction in the duration of catheterization.*

Source: Seguin P, et al. Effectiveness of simple daily sensitization of physicians to the duration of central venous and urinary tract catheterization. *Intensive Care Med* 2010 18 Mar 2010; Epub ahead of print; doi: 10.1007/s00134-010-1829-1.

This study from a surgical ICU in a French university hospital sought to determine the effect on catheterization duration of a daily reminder notifying physicians that the patient had a central venous catheter (CVC) or urinary tract catheter (UTC) and asking whether there was continued need for that catheter. The authors used a before-and-after study design. In the "before" period, the number and duration of CVCs and UTCs in the unit were tracked for a 10-month period, along with the incidence of catheter-associated infections and clinical patient data. For 10

months, starting 2 months after the "before" phase ended, a red box questioning the continued utility of the catheter was added to every daily physician worksheet for all patients with CVCs or UTCs. As part of the routine charting and ordering for each patient every day, the physician was required to check "yes" or "no" to the continued utility of the catheter. If "no" was checked, the nurses in the unit removed the catheter that day.

There were 676 patients in the "before" period and 595 in the "after" period. Duration of catheterization (median [interquartile range]) was significantly less in the "after" period: for CVC, from 5 (3-9) to 4 (3-7) days ($P < 0.001$), and for UTC, from 5 (3-11) to 4 (3-8) days ($P = 0.010$). For CVCs, the incidence of catheter-related infections fell from 1.8% to 0.3% ($P = 0.029$ unadjusted, and 0.010 when adjusted for age, diagnosis, and SAPS II score) in the second study period, although the difference in incidence per 1000 device-days (2.8 vs 0.7) was not different after adjustment as mentioned ($P = 0.051$). For UTCs, the incidence of catheter-related infections was not different (4.3% vs 3.0%; $P = 0.23$ after adjustment), and the same was true for the rate per 1000 device-days (5.0 vs 4.9; $P = 0.938$). The authors conclude that, "This study showed that a simple reminder on the patient's daily care sheet significantly decreased the duration of central venous and urinary tract catheterization."

COMMENTARY

This study has a number of potentially important design problems, the paper omits aspects of the methods and potential discussion points that could have bearing on its validity, and the causality imputed in the authors' concluding statement is assumed rather than demonstrated by the results. In the methods section, the historical baseline durations of CVCs and UTCs in the authors' unit are given as 8 ± 6 and 9 ± 7 days, respectively, yet the observed median "before" rates preceding the intervention described were 5 days in each case. This substantial discrepancy and its relationship to the 1-day average reduction in duration for both catheters following the intervention are not discussed. A concern is that the daily reminder may not have been the only thing different with respect to physicians' tendency to remove catheters sooner than in the past. It is not possible from the information in the paper to assess this or several other questions about the methods, or about other aspects of care in this particular ICU that might have affected the study's findings.

These design and interpretation difficulties notwithstanding, though, the association between the physician reminder and a shorter duration of catheterization supports the notion that changing clinician behavior is an important step in improving outcomes in the ICU. For catheters in ICU patients, time is money. That is, the longer patients have them, the more it costs in terms of the devices and their care, and also in terms of complications. When patients no longer need CVCs and/or UTCs, getting them out as quickly as possible is not only cost-effective but — more importantly — is also better for the patients in several ways.

Special Feature

Less Invasive Hemodynamic Monitoring

By Andrew M. Luks, MD

Intensive care practitioners are constantly faced with questions about their patients' hemodynamic issues, including the volume status, fluid responsiveness, and the need for vasopressors or inotropic support. Because the clinical exam is often of limited utility in addressing these issues, intensivists typically rely on other tools to guide their assessment. For a long time the primary tool for this purpose was the pulmonary artery (PA) catheter, but for a variety of reasons, this device is being used less frequently and clinicians are relying on several less invasive tools for hemodynamic monitoring. The purpose of this special feature is to consider some of these less-invasive systems — the PiCCO™ catheter, the FloTrac™ system, and the LiDCO™ Plus system — in greater detail, reviewing the mechanisms by which the devices derive hemodynamic information, the necessary equipment, limitations of the systems, and the available data regarding their accuracy and utility in the ICU.

What Happened to the PA Catheter?

Before considering these less invasive systems, it is worthwhile to briefly review the issues with the PA catheter that have driven a search for alternatives. The device provides a lot of information including central venous pressure (CVP), PA pressure, pulmonary capillary wedge pressure (PCWP), cardiac output/index (CO/CI), systemic vascular resistance (SVR), and mixed venous oxygen saturation (SvO_2), but it carries significant risks to the patient, including pneumothorax during line placement, arrhythmia, heart block, pulmonary artery rupture, and pulmonary artery infarction.

Aside from concerns about these risks, use of the PA catheter has been declining as a result of several problems. First, evidence suggests that two of the most commonly used pieces of information from the catheter, CVP and PCWP, do not adequately predict fluid responsiveness in hemodynamically unstable patients,[1] and that more dynamic measures, stroke volume variation (SVV), and pulse pressure variation (PPV) — information not avail-

able from a PA catheter — are more useful in this regard.[2] More importantly, multiple studies suggested that use of the catheter was associated with either worse outcomes or no improvement in outcomes in hemodynamically unstable patients, with the final nail in this coffin coming when the randomized, prospective Fluid and Catheter Treatment Trial (FACTT) demonstrated no difference in outcomes in acute lung injury patients managed with a PA catheter or CVP monitoring through a central venous line.[3]

As PA catheter use has declined in response to these concerns, a further insidious effect has taken place, further diminishing the device's utility. Less catheter use has translated into fewer trainees gaining experience with the device and fewer nurses being experienced in how to set up and maintain the system. As a result, each use of the PA catheter becomes an exercise in "re-learning" the tool, with high potential for misinterpreting data or generating misleading information.

Less Invasive Hemodynamic Monitoring Systems

Several less-invasive modalities have emerged for monitoring hemodynamic information and been put forth as alternatives to the PA catheter. While some sources refer to these systems as "non-invasive," the term "less invasive" is more appropriate as the systems still require invasive components including central venous and/or arterial catheters. In the space below, we consider three particular devices that are gaining attention: the LiDCO Plus, the PiCCO catheter, and the FloTrac system. Other less invasive modalities such as transesophageal echocardiography can also be used for hemodynamic monitoring, but will not be considered here because they require more technical expertise and cannot be easily employed in awake patients and, as a result, are less likely to be used as frequently as the systems considered below. The pressure recording analytical method (PRAM)[4] also will not be considered as experience with the system and validation data are both very limited at this time.[5]

The Basics of the Three Systems

LiDCO Plus: The LiDCO Plus (LiDCO Ltd, Cambridge, U.K.) is comprised of two separate components, the PulseCO™ system, which uses arterial waveform analysis to perform continuous CO measurements as well as assessments of SSV and PPV, and the LiDCO system that uses the bolus indicator dilution method to measure CO for the purpose of calibrating the PulseCO system. Use of the system requires a peripheral arterial line and either peripheral or central venous access. Calibration for CO measurements involves injecting small amounts of lithium into the patient's venous access and measuring the decay in lithium concentration at the arterial line. Calibration is typically performed every 8 hours, with any significant hemodynamic change, or before any big change in management.[6] The concentration of lithium (0.15-0.3 mmol for adult patients) is far below therapeutic levels and patients would have to exceed the device's maximum total dose many times before experiencing toxicity.[6] Because of the small concentrations that are used for calibration, the device cannot be used in patients on pre-existing lithium therapy, as it would be impossible to detect the small changes in lithium concentration at the arterial line.[6] It takes only a matter of minutes to connect the patient to the system and begin PulseCO measurements, but lithium calibration adds time to the system set up and often requires additional nursing support, particularly with providers not well versed in its use. Even if lithium calibration is not carried out, however, the PulseCO system can still be used for SVV and PPV assessments. A new LiDCO rapid system has been released, which does not require calibration. A complete review of the device is available elsewhere.[6]

FloTrac: The FloTrac system (Edwards Lifesciences, Irving, CA, USA) uses arterial pressure waveform analysis to provide continuous CO measurements as well as assessments of SVR and SVV. Unlike the LiDCO and PiCCO systems, the FloTrac system requires only an arterial line for operation and purportedly works regardless of the arterial line site. Some data suggest, however, that measurements may be affected by the line's location, particularly in hemodynamically unstable patients or those on vasopressors.[7,8] Another important difference compared to the other systems is that the FloTrac system does not require external calibration. Instead, the system uses demographic data including height, weight, age, and sex in conjunction with arterial waveform analysis to perform its own internal calibration. This is supposed to limit set-up time, an important issue in hemodynamically unstable patients, but may represent a significant limitation if the data used to support the internal calibration were not drawn from an adequately broad population of test subjects, much the same way that utility of "normal" values in pulmonary function testing are limited by the test populations used to generate these values. A complete review of this device is available elsewhere.[7]

PiCCO: The pulse contour cardiac output system (PiCCO; Pulsion Medical Systems, Munich, Germany) also employs arterial waveform analysis, although the algorithm differs from those used by the other systems. It provides similar data as those systems, including PPV, SVV, and CO, but is also able to provide assessments of extravascular lung water and end-diastolic volume. A significant difference with the other systems is the fact that the PiCCO system requires central venous access and a special arterial line that is placed in a major artery (e.g., femoral or brachial) and extends to the central circulation. Peripheral arterial lines cannot be used. External calibration using the saline thermodilution technique is also

necessary and may need to be performed as frequently as every hour in hemodynamically unstable patients.[9] A complete review of the device is available elsewhere.[10]

Available Data Regarding the Utility of the Systems

The key issues with these systems are whether they provide accurate data and make a difference in patient outcomes. Space limitations do not permit a full assessment of the literature available for each system and this discussion will focus, instead, on broad issues in the data. In general, it appears that the PiCCO and LiDCO systems provide reasonably accurate data regarding CO, PPV, and SVV, although the accuracy is likely dependent on the frequency of calibration, particularly in hemodynamically unstable patients.[5] Significant concerns have been expressed, however, about the accuracy of the FloTrac system, especially in hemodynamically unstable patients, although a recent software update may have led to improvements in this regard.[5,7]

A major limitation of the available data, however, is that most of the studies focus on the issue of accuracy and reliability of the systems (e.g., how well do the less-invasive CO readings correlate with invasive measurements using a PA catheter) and we continue to lack data showing that use of these systems in patient management is associated with improvement in patient outcomes such as mortality, length of ICU stay, or time on the ventilator. Given that the demonstrated lack of improvement in patient outcomes started the downward trend in use of the PA catheter, caution is likely warranted before widespread application of these less invasive systems.

Finally, in considering the utility of any new medication or device, it is important to ask whether the studies assessing utility or accuracy are relevant to one's patient population. This turns out to be a big issue with the less invasive monitoring systems as many of the studies have been done in animals or in various patient groups in the operating room (e.g., cardiopulmonary bypass patients), and fewer studies have been done in the setting most relevant to our practice, the ICU.

Important Limitations of the Less Invasive Systems

It is important for clinicians to be aware of several limitations in the applicability of these systems. Because the devices all rely on arterial waveform analysis to generate data, dampening of the arterial signals or significant dysrhythmias will adversely affect the accuracy of the data.[7] For example, atrial fibrillation and the associated alterations in chamber filling time will affect PPV beyond that due to respiratory cycle-induced changes in intrathoracic volume. Other patient factors that affect the character of the arterial pressure waveform, such as aortic regurgitation or use of an intra-aortic balloon pumps, also preclude use.[6] Significant atherosclerosis may also alter the accuracy of PPV measurements by altering arterial compliance and, as a result, pressure variations in response to a given change in stroke volume.[10] This last issue is a tough one to deal with as we lack an easy bedside test to determine whether the patient has significant peripheral atherosclerotic disease and how that will affect measurements.

Another major issue with PPV measurements as well as SVV measurements — two of the important pieces of data provided by these systems not available on a PA catheter — is that they have only been validated for predicting fluid responsiveness in mechanically ventilated patients who are not initiating breaths on their own. As a result, the utility of the devices may be limited in our non-mechanically ventilated patients or those ventilated patients who are not adequately sedated or paralyzed and are making efforts to trigger the ventilator.[10]

Finally, aside from the general issues noted above that apply to each device, there are a few issues that are particular to the LiDCO Plus system. In addition to the fact that it cannot be used in patients on lithium therapy, measurements and calibration are adversely affected by the presence of non-depolarizing muscle relaxants. If such medications are necessary, they should only be given by bolus administration, rather than continuous infusion.[6]

Conclusions

On the surface, the less invasive monitoring systems appear to be an attractive tool for hemodynamic monitoring in the ICU. They involve less patient risk than the PA catheter and, with the exception of the PiCCO system, are generally fast and easy to set up and do not require special invasive lines. They also have the ability to provide data about SVV and PPV, better predictors of fluid responsiveness in mechanically ventilated patients than static measures of volume status such as the CVP or PCWP.[2] The devil is in the details, however. Data exist demonstrating reasonable accuracy and reliability in cardiac output measurements for the LiDCO and PiCCO systems (although concerns still exist about the FloTrac device), but most of these data were not generated in the ICU and we still lack any evidence that using such tools to guide management actually improves outcomes. There are also important limitations with the systems, which, if not recognized at the time the systems are used could lead to erroneous data and misguided patient management.

The concern is that because the devices are easy to set up, nurses and other clinicians will quickly implement them at the bedside, start generating numerical data, and then act on that data before taking time to consider whether aspects of the patient's clinical situation make the data less reliable (e.g., the patient was on a LiDCO Plus while paralyzed for severe hypoxemic respiratory failure). Such details are often overlooked in the chaos surrounding the deteriorating patient.

Until further data are available demonstrating their accuracy and a positive effect on patient outcomes, nurses and intensivists should be measured in their use of these devices. They should not be used in all patients, and are probably best reserved for those with severe hemodynamic issues. Unfortunately, these also happen to be the patients for whom the FloTrac system is considered unreliable and the other systems need more frequent, time-consuming calibration. When these devices are implemented, clinicians should take the time to do the required calibrations, particularly before any big change in management or with any major alteration in patient condition, consider whether patient factors preclude use of the equipment, and always take time to ask whether the data make sense in light of what they are seeing at the bedside with their patient.

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CME / CNE Questions

6. In a recent trial comparing the use of norepinephrine and dopamine in the management of patients with shock, which of the following adverse outcomes was more common in the patients who received dopamine?

a. Atrial fibrillation
b. Skin necrosis
c. Secondary infections
d. Myocardial ischemia

7. Which of the following was observed after patients received a 1.0 µg/kg dose of remifentanil for chest tube removal following cardiac surgery?

a. Near-complete prevention of pain when the tubes were removed
b. Decreases in heart rate and oxygen saturation in comparison with the 0.5 µg/kg dose
c. Apnea and unresponsiveness in 10% of patients
d. All of the above

8. Which of the outcomes are improved as a result of using less invasive hemodynamic monitoring systems in the care of the critically ill?

a. Mortality
b. ICU length of stay
c. Hospital length of stay
d. Duration of mechanical ventilation
e. None of the above

Answers: 6. a, 7. d, 8. e.

CME / CNE Objectives

After reading each issue of *Critical Care Alert,* readers will be able to do the following:

- Identify the particular clinical, legal, or scientific issues related to critical care.
- Describe how those issues affect nurses, health care workers, hospitals, or the health care industry in general.
- Cite solutions to the problems associated with those issues.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Atypical Fractures and Bisphosphonate Therapy

In this issue: Fractures and bisphosphonate therapy, warfarin anticoagulation and influenza vaccine and cotrimoxazole, antiplatelet therapy with clopidogrel and aspirin, FDA Actions.

Bisphosphonates and atypical fractures

Atypical fractures of the femur have been linked with bisphosphonate therapy in several recent news stories. A recent industry-sponsored study looks to quell these concerns. Secondary analysis from three large randomized bisphosphonate trials with more than 14,000 women showed that among 284 hip or femur fractures recorded, a total of 12 fractures in 10 patients were classified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient years. As compared with placebo, the relative hazard ratio for the three trials did not meet statistical significance, although confidence intervals were wide. The authors conclude that the occurrence of fracture of the subtrochanteric or diaphyseal femur was very rare even among women who had been treated with bisphosphonates for as long as 10 years (*N Engl J Med*; published on-line March 24, 2010). An accompanying editorial published on-line at the same time by Elizabeth Shane, MD, Columbia University, acknowledges that despite excellent safety profiles, bisphosphonates have been associated with "atypical" fractures of the femur that occur with minimal or no trauma, generally affecting the proximal third of the femoral shaft. Most of these fractures have occurred in women on long-term alendronate therapy, occasionally taken together with other antiresorptive drugs, corticosteroids, or proton pump inhibitors. Shane points out that while these fractures represent concern, they are uncommon and actually occur more frequently in patients who are not on bisphosphonates. The results of this study "provide assurance that subtrochanteric fractures are extremely rare" and many more hip fractures are "prevented by bisphosphonates than are potentially caused by the drugs." Treatment with bisphosphonates up to 10 years is more effective than shorter-term treatment in preventing new vertebral fractures and nonvertebral fractures, but she also suggests that patients should be considered for "drug holidays with careful observation" if they have been on long-term therapy.

Warfarin, flu vaccine, and cotrimoxazole

Anticoagulation with warfarin requires careful monitoring. Concomitant use of medications may result in changes in the international normalized ratio (INR), which may increase the risk of bleeding or decrease the effectiveness of therapy. Two studies in the April 12 issue of *Archives of Internal Medicine* clarify the risk of two commonly used medications, influenza vaccine and the antibiotic trimethoprim-sulfamethoxazole. Patients on warfarin have been told that they need careful monitoring after the influenza vaccine, although the effect is not clear. Some guidelines have suggested that flu shots prolonged INRs, while others suggest the vaccine reverses the anticoagulation effect.

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In this study, 104 patients on a stable warfarin regimen were randomized to receive influenza vaccine and subsequent placebo administration or vice versa. All patients were tested for coagulation variables and followed for clinical events. The influenza vaccine had no effect on anticoagulation compared to placebo. There were no fatal or major bleeding events. The authors conclude that the influenza vaccine has no significant effect on INR values or warfarin weekly doses in patients on chronic warfarin therapy and that close monitoring of INR values after influenza vaccine is not required (*Arch Intern Med* 2010;170:609-616).

Conversely trimethoprim-sulfamethoxazole (cotrimoxazole) may significantly prolong INRs with adverse clinical outcomes. In the population-based, nested case-controlled study using health care databases in Canada, residents 66 years or older who were treated with long-term warfarin were evaluated for upper gastrointestinal (GI) tract hemorrhage. Of the more than 134,000 patients on warfarin, 2151 patients were hospitalized for upper GI hemorrhage. Recent use of cotrimoxazole was almost four times more common in those hospitalized (adjusted odds ratio, 3.84; 95% CI, 2.33-6.33). The odds ratio for treatment with ciprofloxacin also was higher (1.94), but no significant association was observed with amoxicillin, ampicillin, nitrofurantoin, or norfloxacin. The authors conclude that among older patients receiving warfarin, cotrimoxazole is associated with a significantly higher risk of upper GI tract hemorrhage. Ciprofloxacin was also associated with risk and whenever possible clinicians should prescribe alternate antibiotics in patients receiving warfarin (*Arch Intern Med* 2010;170:617-621).

Clopidogrel and aspirin

What is the optimal duration of dual antiplatelet therapy with clopidogrel and aspirin in patients with drug-eluting stents? In previous studies, early discontinuation of dual antiplatelet therapy has been identified as a risk factor for late stent thrombosis. A new study seeks to determine whether dual antiplatelet therapy for more than 1 year is of value. In a study that merged data from two concurrent randomized, clinical trials, 2701 patients who had received drug-eluding stents and had been free of major adverse cardiac events, cerebrovascular events, or major bleeding for a period of at least 12 months were randomized to receive clopidogrel plus aspirin or aspirin alone. The primary endpoint was a composite of myocardial infarction (MI) or death from cardiac causes. The cumulative risk of the primary outcome at 2 years was 1.8% with dual antiplatelet therapy as compared with 1.2% with aspirin monotherapy (hazard ratio, 1.65; 95% confidence interval, 0.80-3.36; $P = 0.17$). The individual risks of MI, stroke, stent thrombosis, need for repeat revascularization, major bleeding, and death did not differ significantly between the two groups. However, there was a trend toward higher risk for these outcomes in the dual therapy group ($P = 0.051$ for MI, stroke, or death from any cause; $P = 0.06$ for MI, stroke, or death from cardiac cause). The authors conclude that use of dual antiplatelet therapy for longer than 12 months is not more effective than aspirin alone in patients who have received drug-eluding stents (*N Engl J Med* 2010; 362:1374-1382).

FDA Actions

Rifaximin, Salix Pharmaceutical's minimally absorbed (nonsystemic) oral antibiotic has been approved to reduce the risk of recurrent hepatic encephalopathy in patients with advanced liver disease. Rifaximin was previously approved to treat traveler's diarrhea. The drug, which is taken orally twice a day, appears to reduce ammonia levels by reducing gut flora. It is marketed as Xifaxan®.

The FDA has approved Pancreaze, a new pancreatic enzyme product for patients who do not produce enough pancreatic enzymes (due to cystic fibrosis, chronic pancreatitis, pancreatic surgery, etc.). Pancreaze is the third approved pancreatic enzyme product on the market after Abbott's Creon® and Eurand's Zenpep®. The approval coincides with the FDA's deadline to cease marketing unapproved pancreatic enzyme products that have been available for many years. In October 2007, the FDA announced a deadline of April 28, 2010, after which time unapproved products would no longer be available.

The FDA has approved the first generic version of the popular antihypertensive losartan (Cozaar®) as well as the combination of losartan and hydrochlorothiazide (Hyzaar®). This represents the first generic angiotensin receptor blocker on the market, a development that has been anxiously awaited by consumers. Losartan carries a boxed warning against using the drug during pregnancy. Generic losartan is available in 25 mg, 50 mg, and 100 mg strengths, while losartan/hydrochlorothiazide is available in 50 mg/12.5 mg, 100 mg/12.5 mg, and 100 mg/25 mg strengths.