
CRITICAL CARE PHARMACOLOGY LITERATURE UPDATE

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This monthly review of select articles has been compiled and prepared as a service to the members of the Clinical Pharmacy and Pharmacology (CPP) Section of the Society of Critical Care Medicine (SCCM). The content below is for information purposes only and is intended to highlight recent articles that may be of interest to the CPP membership. Though some core content from the publications is presented, the reader is encouraged to review each article in full for additional detail in order to fully interpret the study and its findings.

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INTENSIVE INSULIN THERAPY IN SEVERELY BURNED PEDIATRIC PATIENTS

Jeschke MG, Kulp GA, Kraft R, et al. *Am J Resp Crit Care Med* 2010;182:351-359.

Hyperglycemia in hospitalized patients, when controlled, can improve clinical outcomes as initially shown by Van den Berghe, et al, in adult medical and surgical ICU patients and later in pediatric ICU patients. More recently, however, there have been concerns of an increased risk of hypoglycemic events and related sequelae along with observations of modest clinical benefit. Authors of this paper felt that hyperglycemia associated with severe burns were not addressed entirely by these previous studies and therefore conducted a prospective randomized single-center trial in severely burned pediatric patients. Children were included if they had burns of >30% and required at least 1 surgical debridement. Two hundred thirty nine patients were randomized to a control group (glucose maintained between 140-180 mg/dL, n= 170) or intensive insulin-treated group (glucose maintained between 80-110mg/dL, n= 60). Patients treated with intensive insulin therapy were significantly older and had larger area of third-degree burn. Results showed that the intensive insulin therapy group had significantly decreased incidence of infections and sepsis ($p<0.05$). When comparing hypoglycemic episodes, the control group demonstrated 66 episodes of mild hypoglycemia in 24% of patients and 17 episodes of severe hypoglycemia in 9% of patients, compared to 108 episodes in 43% patients and 23 episodes in 26% patients, respectively, in the intensive insulin therapy group ($p<0.05$). Mild hypoglycemia was defined as <60 mg/dL and severe hypoglycemia as <40 mg/dL, which is consistent with previous trials. The investigators conclude that although hypoglycemic events were more common in the intensive insulin group, there is still a beneficial effect for severely burned patients. Paying attention to iatrogenic causes of

hypoglycemia (i.e., change in nutrition, surgery) and adhering to consistent and validated approaches to controlling blood glucose can aid in controlling hypoglycemic events.

GASTRIC RESIDUAL VOLUME DURING ENTERAL NUTRITION IN ICU PATIENTS: THE REGANE STUDY

Montejo JC, Minambres E, Bordeje L, Mesejo A, Acosta J, et al. *Intensive Care Med* 2010;36:1386-1393.

It has become common practice in the ICU to use gastric residual volume (GRV) as an indicator of enteral nutrition (EN) tolerance. A residual higher than the previously defined normal volume of 200 ml was an indication to hold EN, but this may result in potentially deleterious effects of underfeeding. This study defined high gastric residual volume (HGRV) as 500 ml in the treatment group and 200 ml in the control group. It compared the two with respect to rates of gastrointestinal (GI) complications, diet volume ratio (diet administered compared to diet prescribed), and occurrence of aspiration pneumonia. The study groups were similar at baseline with respect to demographics, admission diagnosis, and acuity of illness scores. The rate of patients achieving the defined HGRV was significantly lower in the treatment group compared to the control group (26.7% vs. 42.4%, $p = 0.003$) while the rates of other GI complications were similar. Diet volume ratio was significantly higher in the treatment group at days 7 and 12 of EN (88% vs. 84% and 88% vs. 86%, respectively), but the difference was not statistically significant after the 2nd week. There was no difference in occurrence of pneumonia between groups (28% vs. 27.3%). This study suggests that increasing the threshold for HGRV may allow for delivery of a greater proportion of prescribed EN without an increase in adverse events including aspiration pneumonia.

A MULTI-CENTER RANDOMIZED, DOUBLE-BLIND, PARALLEL, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF INTRAVENOUS IBUPROFEN FOR THE TREATMENT OF FEVER IN CRITICALLY ILL AND NON-CRITICALLY ILL ADULTS.

Morris PE, Promes JT, Guntupalli KK, et al. *Critical Care*. 2010;14:R125.

One limitation of nonsteroidal anti-inflammatory drugs (NSAIDs), with the exception of ketorolac, which has its own associated risks, is their exclusive availability as oral entities. This study, which was undertaken to assess the efficacy and safety of intravenous ibuprofen, enrolled 120 hospitalized patients – at least a third of whom were critically ill (mechanically ventilated, requiring pressor support, or both), and at least a third of whom *were not* – with single temperatures of 101°F or greater. Patients were randomized to receive either placebo (n=28) or one of three intravenous ibuprofen doses [100 mg (n=31), 200 mg (n=30), or 400 mg (n=31)] every 4 hours for 24 hours. Although there were no differences in baseline characteristics among groups, a significantly higher number of patients in the ibuprofen arms achieved temperatures less than 101°F within four hours after the first drug dose as compared to placebo (77% [400 mg] vs. 9% [placebo]; p=0.0005; 70% [200 mg], 61% [100 mg] vs. 9% [placebo]; p = 0.0264). Euthermia over the 24 hour observational period was only maintained in the 400 mg arm. A subgroup analysis of the critically ill patients in the sample noted lower serum ibuprofen concentrations and extent of temperature reductions as compared to the non-critically ill population. While IV ibuprofen *was not* associated with worsening renal function or a higher risk of bleeding, the study was limited by its short duration

and small size, making it difficult to rule out the possibility of a clinically significant elevated risk. While this trial indicates that IV ibuprofen is safe and effective when given for a single day, studies evaluating the safety of use for longer periods of time would be helpful to compare the safety with that of IV ketorolac.

EARLY ADMINISTRATION OF NOREPINEPHRINE INCREASES CARDIAC PRELOAD AND CARDIAC OUTPUT IN SEPTIC PATIENTS WITH LIFE-THREATENING HYPOTENSION

Hamzaoui O, Georger JF, Monnet X, Ksouri H, Maizel J, et al. *Critical Care* 2010;14:R142

The objective of this observational, single-center, clinical trial was to examine the cardiac consequences of norepinephrine administration in severely hypotensive septic patients. Inclusion criteria were receipt of norepinephrine to achieve a MAP > 65 mmHg within 6 hours of admission to the ICU. Patients were excluded if they required simultaneous administration of other vasopressors, new fluid challenges or blood transfusions, or required modification of ventilator settings or sedatives during the study period. Hemodynamic parameters were measured in triplicate before and after initiation or dose adjustment of norepinephrine. In 105 patients, norepinephrine introduction (or dose increase) to achieve MAP > 65 mmHg significantly increased cardiac index (3.2 ± 1.0 to 3.6 ± 1.1 L/min/m²), stroke volume index (34 ± 12 to 39 ± 13 mL/m²), goal end-diastolic volume index (694 ± 148 to 742 ± 168 mL/m²), and cardiac function index (4.7 ± 1.5 to 5.0 ± 1.6 min⁻¹). In 59 mechanically ventilated patients where stroke volume variation (SVV) was recorded, norepinephrine significantly decreased SVV from $13 \pm 6\%$ to $9 \pm 5\%$. The median MAP achieved after norepinephrine introduction/increase was 75 mmHg. In 71 patients with an LVEF >45%,

norepinephrine significantly increased CI, SVI, and GEDVI. Thirty-four patients with an LVEF \leq 45%, norepinephrine had significantly increased CI, SVI and GEDVI; however, these effects were not found in the subgroup of 17 patients with an achieved MAP \geq 75 mmHg. Norepinephrine administration in severely hypotensive septic patients results in increased cardiac output. These positive effects can be seen in patients with poor cardiac contractility, except when MAP exceeds 75 mmHg.

PROTOCOLIZED INTENSIVE CARE UNIT MANAGEMENT OF ANALGESIA, SEDATION, AND DELIRIUM IMPROVES ANALGESIA AND SUBSYNDROMAL DELIRIUM RATES

Skrobik Y, Ahern S, Leblanc M, Marquis F, Awissi D, et al. *Anesth Analg* 2010;111:451-63.

The members of this multidisciplinary group developed a symptom guided, nurse administered analgesia, sedation, and delirium management protocol to be used on all patients within a mixed medical/surgical intensive care unit. The primary hypothesis was that, by distinguishing the clinical features of pain, sedation, and delirium, a pharmacologic and non-pharmacologic pathway would result in reduced medication use and improvements in clinical outcomes. Prospective data collection occurred on 572 pre-implementation (PRE) patients and 561 post-implementation (POST) patients. Once per shift nurses would assess for pain (NRS or BPS converted to NRS for unresponsive patients), sedation (RASS), and delirium (ICDSC). The results of the rating scales were used to drive medication use in the POST patients – the protocol used is provided in the appendix of the article. The investigators found that the POST cohort achieved better analgesia while requiring significantly lower doses of opiates; mean opiate doses were 4-fold less in those receiving opiates. Benzodiazepine use was slightly lower, and significantly fewer patients

received propofol. Drug management with antipsychotics did not differ between the groups. Important clinical outcomes that favored the use of the protocol included reductions in medication induced coma, ICU LOS (6.3 vs. 5.35 days, $p=0.009$) and LOS (55 vs. 27 days, $p<0.0001$), and duration of mechanical ventilation (7.5 vs 5.9 days, $p=0.01$). Additional subgroup analyses are also reported. Non-pharmacologic means for providing symptom relief included music and reassurance. Although the effects of these methods are difficult to quantify, the investigators believe that these approaches can be beneficial in the critically ill.



GUIDELINES UPDATE

AHA/ASA Guideline: Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. *Stroke* 2010;41:2108-2129.



CONTRIBUTORS

Ifeoma Asoh, PharmD (UMass); Marcus Costner, PharmD, BCPS (VA); Erin Frazee, PharmD (Mayo); Haley Goodwin, PharmD, BCPS (Johns Hopkins); Deanna McMahon Horner, PharmD, BCPS (UCSF); Emily Hutchinson, PharmD, BCPS (Methodist); Erin Koopman, PharmD, BCNSP (Mayo); Shawn Kram, PharmD, BCPS (Via Christi); Jessica Mercer, PharmD (MUSC); Heather Personett, PharmD (Mayo); Angela Plewa, PharmD, BCPS (Stroger); Bridgette Therriault, PharmD (Wesley); Charles J Turck, PharmD, BCPS (UMass); Peter Herout, PharmD, BCPS (EPI-Q, Inc.).