

Commentary

Recently published papers: Out with the old and in with the new ... then something new for the old!

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Published online: 12 May 2005

This article is online at <http://ccforum.com/content/9/3/238>

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Critical Care 2005, **9**:238-240 (DOI 10.1186/cc3723)

Abstract

New therapies are challenging older, established practices. One recently published report shows us that we may be able to avoid endotracheal intubation in patients with a reduced level of consciousness. Recombinant activated factor VII is proving to be useful in many coagulation disorders, and intracerebral haemorrhage can be added to this list. Homeopathy, in the form of potassium dichromate, shows promise as a new treatment for excessive tracheal secretions. Rotation protocols for antibiotics have been evaluated with respect to their ability to prevent the development of new resistant micro-organisms in our hospitals and units. Finally, glucocorticoids may be of benefit to septic patients outside the intensive care unit (ICU) and may prevent their deterioration and admission to the ICU.

Intensive care medicine is a relatively new medical speciality and so it is inevitable that established practices based on expert opinion (level V evidence) will be challenged. The use of noninvasive positive pressure ventilation (NiPPV) to treat acute respiratory failure (ARF) is a treatment that is often contraindicated in patients with reduced consciousness level because of the risk for aspiration. This concept has been challenged by Diaz and coworkers [1] in a recent report published in *Chest*. Those investigators conducted a prospective, open, uncontrolled study to assess primarily the success (defined as avoidance of endotracheal intubation, and survival to 24 hours after intensive care unit [ICU] discharge) of NiPPV therapy for ARF in patients with a Glasgow Coma Scale (GCS) score of 8 or below versus those with a GCS score above 8. Secondly, they aimed to identify variables that would predict failure of NiPPV in these patients.

A total of 958 patients were recruited into the study, of whom 95 had a GCS score of 8 or below [1]. The results revealed greater success for NiPPV in the comatose group (80.0% versus 70.1%; $P=0.043$). However, ARF secondary to

chronic obstructive airways disease (COAD) appeared to respond better than ARF of other causes, such as acute respiratory distress syndrome and pneumonia, and this was seen in a higher percentage of the comatose group, which might have accounted for the better outcome. Hospital mortality was similar between groups. Of the 95 coma patients recruited, aspiration occurred once, and this patient went on to require intubation. Factors predicting hospital survival in the comatose patients included a lower Acute Physiology and Chronic Health Evaluation II score and respiratory rate, as well as initiation of therapy in the emergency department rather than in the ICU. This paper provides further evidence of the importance of early initiation of therapy, before ICU admission, as was described in the landmark report by Rivers and coworkers [2].

Recombinant activated factor VII (rVIIa), although not yet widely used, is a new drug that may be considered in the management of many types of bleeding and coagulation disorders in the future. Because of the new surface-based model for coagulation and the important role that factor VII plays in this [3], we can appreciate how rVIIa can overcome a number of coagulation deficits. Mayer and coworkers [4] investigated its use in patients with acute intracerebral haemorrhage – a condition associated with high rates of mortality and morbidity. Because surgical intervention is not always possible, pharmacologically reducing the size of the haematoma is an attractive option.

In their multicentre, double-blind, placebo-controlled trial, Mayer and coworkers [4] randomly assigned 399 patients into four groups: one placebo group and three rVIIa groups (40, 80 and 160 µg/kg). The results showed that the percentage increase in the volume of haematoma was significantly lower in the three rVIIa groups combined

ARF = acute respiratory failure; COAD = chronic obstructive airways disease; F_{iO_2} = fractional inspired oxygen; GCS = Glasgow Coma Scale; ICU = intensive care unit; NiPPV = noninvasive positive pressure ventilation; P_{aO_2} = arterial oxygen tension; rVIIa = recombinant activated factor VII.

compared with placebo ($P=0.004$). However, when these groups were compared individually with placebo, only in the the group receiving 160 $\mu\text{g}/\text{kg}$ was the difference significant. Secondary outcomes (90-day mortality: 29% placebo versus 18% combined rVIIa; and 90-day severe disability: 69% placebo versus 53% combined rVIIa, $P=0.004$) were also significantly lower in the combined rVIIa group. A subgroup also emerged in which these significant differences were only noted if the rVIIa was administered within 3 hours of the occurrence of symptoms. Thromboembolic complications, a concern with the use of rVIIa, occurred in 7% of the rVIIa group and 2% of the placebo group ($P=0.12$). In the placebo group these were all venous in origin and not serious, whereas in the rVIIa group most were arterial. Of these the most common were cerebral infarction, of which two were fatal, followed by myocardial infarction, most of which were followed by good recovery.

Fass and coworkers [5] investigated the use of potassium dichromate, a drug that is used in homeopathy for its mucolytic properties in sinusitis [6], in patients with a history of COAD and tobacco use within the preceding 10 years, who would expected to be slow to extubate because of tenacious, stringy tracheal secretions. A total of 50 patients were investigated in that prospective, randomized, double-blind, placebo-controlled study. Extubation was considered difficult in this patient group primarily because of excessive secretion production. The amount of secretions was recorded (a grading system according to the volume produced was used to compare secretion production) as well as the time to extubation and length of stay. All were significantly decreased in the potassium dichromate group. Interestingly, β_2 -agonists (standard treatment for COAD) were stopped for the duration of the study to avoid any influence on or interference with treatment. Potassium dichromate can cause multisystem toxicity and allergic sensitivities if it is administered undiluted, but it was not found to be harmful in the diluted homeopathic doses used in this study. The authors claim that this is the first scientific study of the effect of potassium dichromate on secretions; the results are welcome and warrant further study because *N*-acetylcysteine, which has traditionally been used, is associated with allergic complications in intensive care staff.

Multiresistant Gram-negative micro-organisms are becoming a serious issue in many ICUs. Apart from instituting strict infection control regimens, can we help to control their development with antibiotic protocols? Loon and coworkers [7] investigated the effects of antibiotic cycling in their eight-bed surgical ICU. They cycled antibiotic treatment for suspected Gram-negative infections over periods of 4 months, using agents from two different classes (quinolones and β -lactams), representing two different mechanisms for development of resistance. The primary end-point was acquisition rate of Gram-negative bacteria resistant to the current cycled antibiotic, and secondary end-points were

changes in endemic prevalence of resistant bacteria and the relative importance of cross-transmission.

A total of 341 patients were included in the study over a 16-month period (four cycles), and in 95.6% of cases antibiotics were prescribed according to the study protocol [7]. The results showed that exogenous acquisition (defined as acquisition of a micro-organism isolated from another patient present on the ward within a certain time frame) decreased over time, and endogenous acquisition (colonization of a micro-organism of a new genotype) remained the same. The number of resistant organisms developing to the antibiotic of a cycle did not immediately decrease following the start of a new cycle, as would be expected. Loon and coworkers suggest that factors influencing their results include an increase in the prescription of antibiotics during the study, which might have been due to the protocol prescription, decreasing microbiology input on ward rounds, and the inability to prevent cross-transmission completely. However, they feel that antibiotic cycling was not proven to be beneficial in the study, and that stricter prescribing of antibiotics and infection control may be the way forward in this field.

Steroid therapy has been widely accepted as representing essential management in the patient with vasopressor-dependent septic shock [8], and therefore it comes as no surprise that glucocorticoids may be of benefit to patients outside the ICU. Research has shown that 'nonsurviver' patients compared with 'survivor' patients with community-acquired pneumonia have higher levels of circulating cytokines [9]. Confalonieri and coworkers [10] reported a preliminary randomized study investigating steroid use in patients requiring ICU treatment for community-acquired pneumonia. Primary end-points were arterial oxygen tension (PaO_2)/fractional inspired oxygen (FiO_2) ratio, multiple organ dysfunction score and development of delayed septic shock, and secondary end-points included duration of stay in critical care and mechanical ventilation, and survival to hospital discharge and at 60 days. The trial recruited patients with severe community-acquired pneumonia using criteria from the American Thoracic Society. In the treatment group hydrocortisone was given, initially as a bolus, followed by a low-dose infusion. However, exclusion criteria included a requirement for more than 0.5 mg/kg per day prednisolone equivalent for any reason, including bronchospasm. Antibiotic treatment followed the American Thoracic Society Guidelines.

The study was powered to detect an improvement in $\text{PaO}_2/\text{FiO}_2$ ratio and was stopped when this was achieved after 46 patients were recruited [10]. $\text{PaO}_2/\text{FiO}_2$ ratio was found to be statistically better in the hydrocortisone group, and hospital mortality, duration of mechanical ventilation, C-reactive protein and delayed septic shock were statistically reduced, although these findings might have been biased by the small sample size. Despite some imbalances between the placebo and treatment group characteristics, the authors

stress that early treatment with glucocorticoids and use of a continuous infusion could account for the positive findings in their trial compared with previous ones and that further investigation is warranted.

Competing interests

The author(s) declare that they have no competing interests.

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