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Prehospital Aspirin Use and ARDS – A Case for Aspirin in the Drinking Water?

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In this issue of *Critical Care Medicine*, Chen and colleagues present a cross-sectional analysis demonstrating that prehospital aspirin use is associated with a significant decrease in the incidence of acute respiratory distress syndrome (ARDS) during the first four days of ICU admission, adjusting for the propensity to receive aspirin (1). Preclinical data have suggested a potential role for platelet inhibition in preventing acute lung injury (2-4). Multiple observational studies examining the association between aspirin therapy and the development of ARDS have had inconclusive results (5-7). The largest study to date by Kor et al used propensity matching to balance potential confounding variables between aspirin users and non-users and concluded that prehospital aspirin therapy did not reduce the risk of lung injury (6).

The study by Chen et al has several important strengths. First, the investigators limited this analysis to a more homogenous group of lung injury patients by excluding trauma and surgical patients. Trauma and surgical patients may have unreliable medication histories or indications to discontinue aspirin therapy prior to admission. Second, the VALID cohort has been NIH funded as a prospective cohort study with very detailed phenotyping of lung injury by experts. Therefore, misclassification of their outcome is minimized, and should not be influenced by such factors as heart failure, which could in turn be related to aspirin use. Third, the cohort used for this analysis also has a much higher incidence of ARDS with 32% developing ARDS within four days of ICU admission (compared to 6.2% in the Kor et al study). With a more enriched sample, Chen and colleagues detected a benefit to aspirin therapy that the Kor et al study may not have been powered to detect. Fourth, the authors' propensity adjustment methods employed a large and well-thought-out list of clinical

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variables, and thus yield the best possibility of addressing potential effects of confounding by indication for aspirin use.

In general, medication use is one of the more difficult variables to classify in observational studies, where such variables as dosage level, time from drug administration to outcome (ARDS), and adherence to therapy may cause misclassification of the nature of the exposure. Biologically, one would like to know whether aspirin effect was present in the blood of patients before development of ARDS, but these methods are costly, and cumbersome. In the current study by Chen and colleagues, the authors did a very good job of ascertaining aspirin exposure, given the inherent limitation of cohort studies such as theirs. Nonetheless, since both aspirin use and ARDS were determined at the same point of time for the vast majority of patients, the assumption is that patients were using aspirin therapy prior to hospital admission. Medication discrepancies are common at the time of hospital admission, including both errors of commission and omission, (8,9) and this may be more significant with an over-the-counter medication such as aspirin. It is unknown if misclassification of aspirin use is different between ARDS and non-ARDS patients. Perhaps those developing ARDS on the first ICU day were too ill to communicate their medications accurately and were not taking aspirin as prescribed or, alternatively, buying aspirin over-the-counter. In addition, the observational nature of this analysis does not provide us with information about the duration of aspirin use prior to admission or the actual effect of aspirin on the platelet function of an individual patient. We can thus conclude from the results of the VALID study that a medication list including aspirin is associated with decreased odds of developing ARDS in this cohort of patients. Short of a randomized clinical trial, this is about the best we can do.

As the authors comment, there is an ongoing multicenter, randomized control trial (NCT101504867) designed to evaluate aspirin for the prevention of ARDS – Lung Injury Prevention with Aspirin (LIPS-A) (10). The results of the Chen et al study in this issue of *Critical Care Medicine* raise several concerns about the design of the LIPS-A trial. As Chen and colleagues discuss, the majority (84%) of patients in this observational study presented with ARDS on the first ICU day. A similar finding has been reported in other cohorts (11,12) including a cohort of patients with sepsis at our institution (unpublished data). In the LIPS-A trial, patients are randomized to receive aspirin within the first 24 hours after hospital presentation. A key exclusion criterion is antiplatelet therapy in the previous 7 days. The LIPS-A trial is thus designed to answer a very different question than that studied by Chen et al. It is certainly possible that the benefit to anti-platelet agents are only seen when this therapy is initiated prior to the insult resulting in lung injury. The insult that resulted in the lung injury – the infection leading to sepsis, the development of pancreatitis, the traumatic event – occurred prior to the time of randomization and thus prior to aspirin therapy. Herein lies the challenge in preventing ARDS. In a significant (if not majority) of patients, ARDS is present at the time of presentation. A randomized, controlled trial of aspirin therapy versus placebo prior to the inciting event is obviously infeasible.

The study by Chen and colleagues uses rigorous methodology to evaluate the role of aspirin in the prevention of ARDS. Despite the possible misclassification of the exposure variable common to all such studies, the results are robust and argue for the potential benefit of anti-

platelet therapy in halting the progression of acute lung injury. Unfortunately, the clinical application of these results remains challenging. We do not know who would gain the greatest benefit from starting aspirin therapy because we currently do not have the ability to predict who will develop a clinical condition that increases his/her risk of developing ARDS. Also, it is difficult to argue for universal aspirin use in the general population given potential side effects in long-term users. Preclinical studies on the potential benefit of aspirin therapy in preventing lung injury are promising and now supported by this study, but the practical application of administering aspirin to patients prior to the development of ARDS remains daunting.

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