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Effects of Pre-Hospital Antiplatelet Therapy on the Incidence of ARDS

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BACKGROUND: Clinical observations on the potential of pre-hospital antiplatelet therapy in preventing ARDS have been inconsistent. To further the correlation between antiplatelet therapy and ARDS, we conducted a meta-analysis to evaluate the effects of pre-hospital antiplatelet therapy on subjects with ARDS. METHODS: A literature search in major data banks was performed. We included prospective and retrospective cohorts, case-control trials, and randomized controlled trials that compared the ARDS incidence in subjects with or without pre-hospital antiplatelet agents. RESULTS: Meta-analysis of 7 studies (a total of 30,291 subjects) showed significantly lower odds of ARDS in the pre-hospital antiplatelet therapy group compared with subjects with no pre-hospital antiplatelet therapy (odds ratio 0.68, 95% CI 0.56–0.83; *P* < .001). However, ARDS mortalities in the hospital and ICUs were not affected. CONCLUSIONS: These findings indicated that pre-hospital antiplatelet therapy was associated with a reduced rate of ARDS but had no effect on the mortality in the subjects at high risk. *Key words: anti-platelet agents; ARDS; aspirin; intensive care; morbidity; pre-hospital antiplatelet therapy.* [Respir Care 0;0 (0):1–●. © 0 Daedalus Enterprises]

Introduction

ARDS is a serious complication of acute illness and injury that is associated with an in-patient mortality of up to 40%.[1] The age-adjusted incidence of ARDS was 27.6 cases per 100,000 person-years,[2] with European countries reporting a lower incidence than the United States.[3] Patients with ARDS may continue to experience impaired pulmonary function and a low quality of life after hospitalization.[4] ARDS can be associated with elective surgery, surface burns, acute pancreatitis, trauma, or amniotic fluid embolism.[5,6] Despite considerable research efforts, established therapeutic strategies for ARDS are limited.[7]

Antiplatelet drugs, including aspirin and P2Y12 receptor inhibitors, are commonly used for secondary prevention of atherothrombotic events in patients with cardiovascular diseases. Aspirin and clopidogrel (P2Y12 receptor inhibitor) also reduce systemic inflammation and platelet-leukocyte coagulation, both of which are implicated in ARDS pathogenesis.[8,9] Excess inflammation in ARDS due to increased pulmonary capillary permeability or dysregulated platelet aggregation can result in alveolar damage and a consequent reduction in lung compliance.[10] There is ample evidence that platelets play an important role in the development of

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ARDS. For example, platelets promote leukocyte migration and recruitment by releasing chemokines, such as chemokine (C-X-C motif) ligand 4, and delivering leukocyte-binding proteins to endothelial cell surfaces, thereby forming a pro-inflammatory milieu.[11,12] Platelets have been shown to generate microparticles, which are found to interact with vascular endothelium and neutrophils to modulate inflammation and immune responses in the lungs.[13] The activation of neutrophil extracellular traps is another mechanism by which platelets mediate inflammation. Neutrophil extracellular trap formation induces the death of neutrophils and, in turn, leads to exaggerated inflammation in conditions such as ARDS.[14] Animal models also support the use of antiplatelet therapy for ARDS. It has been indicated that the inhibition of platelet-neutrophil aggregates can be effective in the prevention of ARDS.[15]

Results of a study of small samples suggest that administration of aspirin within 24 h of emergency department presentation did not reduce the risk of ARDS at 7 days for those subjects at risk of ARDS.[16,17] However, whether pre-hospital antiplatelet therapy elicits beneficial effects in patients with ARDS who are critically ill remains controversial.[18-20] Therefore, we performed a meta-analysis and provided an update on the scientific literature to explore the effect of pre-hospital antiplatelet drugs on the incidence of ARDS. Our key objectives were to determine if pre-hospital antiplatelet therapy is associated with decreased ARDS risk and ARDS-related mortality in subjects at high risk.

Methods

Search Strategy and Selection Criteria

We searched major medical bibliographic databases, including PubMed, Web of Science, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews, for observational studies that reported on the association between pre-hospital antiplatelet therapy and the risk of ARDS from January 1980 to July 2019. We used Boolean logic, with search terms that included "pre-hospital," "anti-platelet drugs," "anti-platelet agents," "aspirin," and "acetyl salicylic acid," combined with "ALI (acute lung injury)," "acute lung injury," "ARDS," and "acute respiratory distress syndrome." Controlled vocabularies, such as Medical Subject Heading terms, were used to identify synonyms.

All human studies that were published in full text, abstract, or poster form were eligible for inclusion. The Conference Papers Index provided by ProQuest (ProQuest LLC, Ann Arbor, Michigan) was used to search conference posters and abstracts (1980–present). These studies included randomized controlled trials (RCT) and other comparative study designs that were conducted in subjects at high risk of developing ARDS. The last search date was July 31, 2019. We included studies that involved participants ≥18 y old with a history of pre-hospital antiplatelet therapy and development of ARDS. We excluded studies if they involved subjects ≤18 y or noncontrol studies. Each study was independently screened and determined for eligibility by two of us (WJ, HJ).

Data Extraction and Validity Assessment

Two of us (WJ, HJ) independently extracted data (in duplicate) from all included studies by using a template adapted from the Cochrane Collaboration. For each study, we extracted the study design, number of subjects, age of the subjects, population, antiplatelet agents, number of subjects with pre-hospital antiplatelet therapy, morbidity and mortality of ARDS, and the primary causes for ARDS.

Assessment of Bias Risk

The risk of bias was independently evaluated by two of us (WJ, HJ). We used the Newcastle-Ottawa scale to assess the quality of nonrandomized cohort or case-control studies, as suggested by the Cochrane Collaboration. Study quality was determined by a star system in which each study was judged on 3 domains: the selection of the participants, comparability of the study, and ascertainment of either the outcome (for cohort) or exposure (for case-control studies) of interest. These domains were composed of 8 established assessment questions, with a star awarded to each high-quality response. Studies that received a total of ≥6 stars were considered to be of high quality or have a low risk of bias.

Definition of Control or Treatment Groups

Treatment groups involved the subjects who received the antiplatelet agents (eg, aspirin and clopidogrel bisulfate) before hospital admission. The dose of aspirin ranged from 75 to 300 mg daily, and, for clopidogrel, 75 mg daily. The control group consisted of subjects without pre-hospital antiplatelet therapy. If studies included both adults and children, only the details of adult subjects were extracted. Similarly, if the treatment group included subjects diagnosed with ARDS at admission in prospective cohort studies, we excluded these data from the morbidity analysis.

Definition of Outcomes

The primary outcome was the occurrence of ARDS, which was defined by using the 1994 Standard American-European Consensus Conference criteria or the 2012 Berlin definition.[21] ARDS is a diffuse, inflammatory lung injury, which leads to increased pulmonary vascular permeability,

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increased lung weight, and loss of aerated lung tissue, that is associated with increased physiologic dead space and decreased lung compliance. The definition of ALI had been replaced by ARDS according to the Berlin consensus.[21] The occurrence of ARDS, including ALI, was determined based on diagnosis reports provided by each study. If a study reported lung dysfunction, then we collected and analyzed data details for diagnosis. Studies were excluded if these data were not available.

Statistical Analysis

Statistical analyses were performed by using RevMan 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration). A random-effects model was used to calculate odds risks (OR) with 95% CI for dichotomous data. Outcome measures were quantitatively summarized. Treatment effect estimates were calculated by using the Mantel-Haenszel test in which an OR < 1 suggested a decreased risk of ARDS compared with the control. Heterogeneity among combined study results was evaluated by Cochrane's Q statistic and the I^2 statistic. A value of $>50\%$ indicated moderate to high heterogeneity. Furthermore, we sought potential explanations for this degree of statistical heterogeneity by using sensitivity analysis. We also conducted subgroup analyses to establish whether a different study design affected our conclusions. Statistical significance was set at the 2-tailed 0.05 and 0.10 levels for hypothesis and heterogeneity testing.

Results

A total of 235 unique articles, including conference abstracts, were identified by our searches (Fig. 1), and 7 articles that involved 30,291 subjects fulfilled the eligibility criteria for analysis (Fig. 1).[18-20,22-25] Three studies were prospective cohort investigations, 3 were retrospective cohort investigations, and one was a retrospective nested case-control study. These studies were performed in various sample sizes (ranging from 141 to 23,882 subjects), populations, and care settings (Table 1). The Newcastle–Ottawa scale was used to evaluate study quality and the risk of bias in cohort studies. Studies included were generally of high quality, as shown in Table 1.

One study (Mazzeffi et al[20]) defined ARDS by using the Berlin definition, and another study (Tuinman et al[24]) used the 2004 consensus of transfusion-related ARDS. The remaining 5 studies diagnosed ARDS according to the criteria of the 1994 American-European Consensus Conference on ARDS.[18,19,22,23,25,26] Three studies included medical ICU subjects.[22,23,25] Other studies included subjects with major risks for ARDS (eg, sepsis, pneumonia, shock, pancreatitis) and subjects undergoing aortic valve replacement surgery or transfusion.[18-20,24]

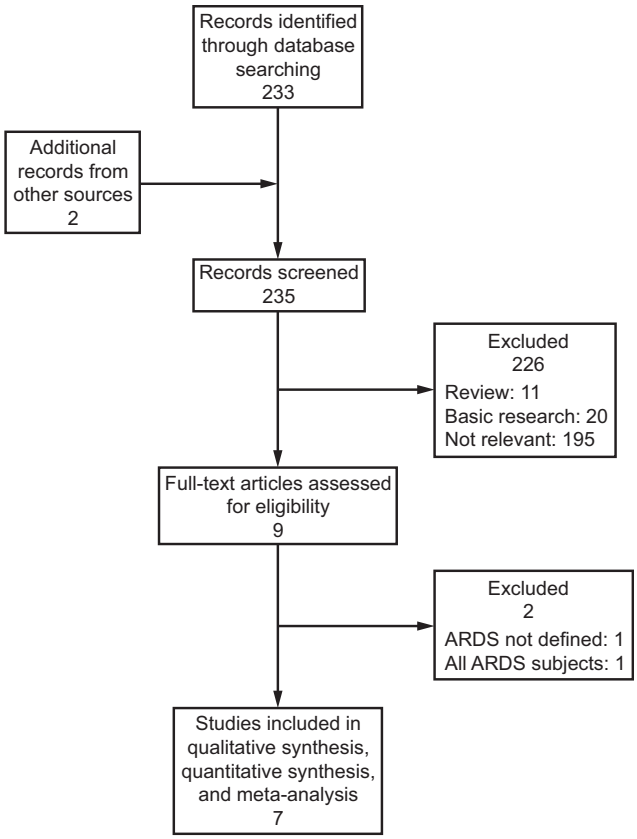

Fig. 1. Flow chart.

Mazzeffi et al[20] and Gross et al[25] explicitly reported aspirin use for >5 d before surgery and clopidogrel use for at least 6 consecutive prescriptions preceding community-acquired pneumonia, respectively. Meta-analysis of 7 studies[18-20,22-25] revealed an association between pre-hospital antiplatelet therapy and decreased odds of ARDS (OR 0.68, 95% CI 0.56–0.83; $P < .001$) (Fig. 2).

Antiplatelet drugs include aspirin, clopidogrel, and ticlopidine. In fact, the main antiplatelet drug used in the market was aspirin or a related combination with other drugs. All the data were combined and analyzed together with these references. According to Figure 2, there was a marked decrease in ARDS with antiplatelet therapy usage. Minimum heterogeneity was noted across the studies ($I^2 = 34\%$). The crude hospital mortality in the pre-hospital antiplatelet therapy was not significantly different from that in the non-antiplatelet therapy group (OR 0.85, 95% CI 0.68–1.06; $P = 0.16$, $I^2 = 7\%$) (Fig. 3). Although antiplatelet therapy has anti-inflammatory effects for subjects with early stage ARDS, it does not have marked effects in later stage, which accounts for nonsignificance in such mortality. Three studies that calculated ICU mortality showed a crude mortality of 5.58% and 5.66% in the pre-hospital antiplatelet therapy users and nonusers, respectively (OR 0.84, 95% CI 0.63–1.11; $P = .22$, $I^2 = 0\%$).[18,22,23]

RESPIRATORY CARE Paper in Press. Published on February 11, 2020 as DOI: 10.4187/respcare.07177

Table 1. Characteristics of Studies Included in the Meta-Analysis

Study	Design	Single Center/Multi Center	Study Location	Subjects, *n*	Age, y	Study Population	Antiplatelet Agents	Newcastle–Ottawa Scale Score*		
								Selection	Comparability	Exposure/ Outcome
Chen et al, [19] 2015	Prospective cohort	Single center	USA	1,149	≥40	High risk for ARDS in ICU	Aspirin	****	*	***
Erlich et al, [22] 2011	Prospective cohort	Single center	USA	161	≥18	Medical ICU admission with at least one major risk factor for ARDS	Aspirin, anagrelide, clopidogrel bisulfate	***	*	***
Mazzeffi et al,[20] 2015	Retrospective cohort	Single center	USA	375	Adult	After aortic valve replacement surgery	Aspirin	**	*	***
Kor et al,[18] 2011	Prospective cohort	International multi-center	USA and Turkey	3,855	Adult	Nonsurgical subjects with at least one major risk factor for ARDS	Aspirin	****	*	***
Tuinman et al,[24] 2012	Retrospective, nested case-control study	Single center	Holland	218	Adult	Transfusion related	Aspirin	***	*	***
Gross et al,[25] 2013	Retrospective cohort	Single center	USA	23,882	Adult	In-patients with CAP	Clopidogrel	***	*	***
Valerio-Rojas et al,[23] 2013	Retrospective cohort	Single center	USA	651	Adult	Adult subjects with severe sepsis or septic shock	Aspirin (88.6%) or aspirin + clopidogrel (9.9%)	***	*	***

*, basic evaluation of the study quality; **, intermediate evaluation of the study quality; ***, highly regarded evaluation of the study quality; ****, the highest evaluation of the study quality. Note, all are based on Newcastle-Ottawwa Scale as mentioned in the table.
CAP = community-acquired pneumonia

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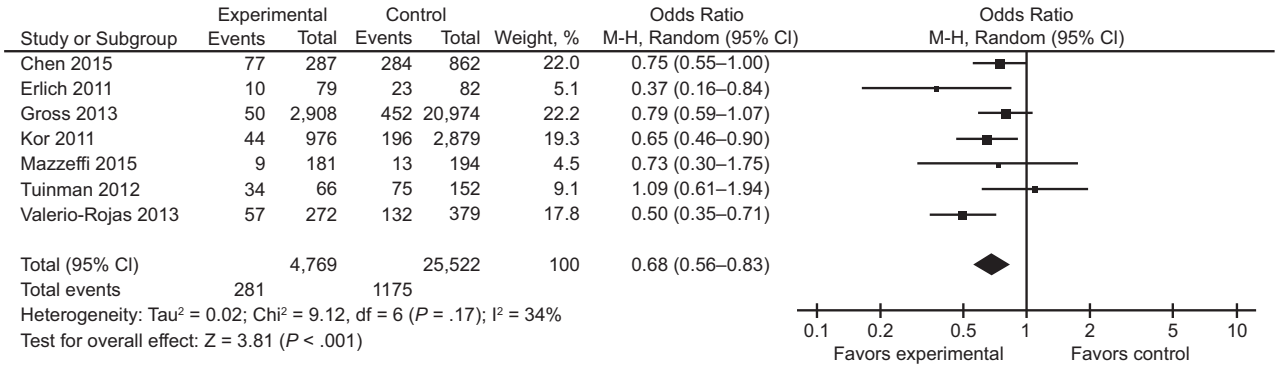

Fig. 2. Morbidity of ARDS in subjects receiving pre-hospital antiplatelet therapy (APT) versus without APT. Forest plot showed odds of development of ARDS in subjects with or without pre-hospital APT.

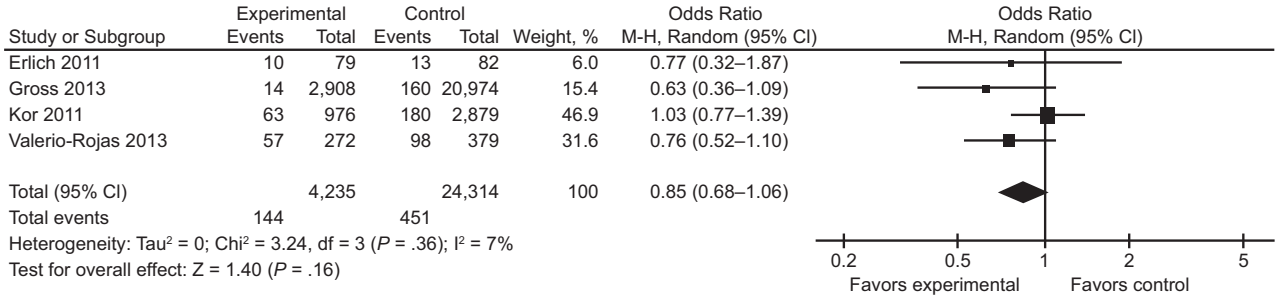

Fig. 3. Mortality difference between subjects receiving pre-hospital antiplatelet therapy (experimental) versus those without (control).

Of 4,769 subjects with antiplatelet therapy, 3 took clopidogrel, one took anagrelide, 27 took both aspirin and clopidogrel, and the remaining took aspirin solely. Among the aspirin users, 621 subjects took aspirin at a dose of <100 mg/d and 92 subjects at a dose >300 mg/d, and 1,296 subjects were not mentioned. One study showed that the dose of pre-hospital aspirin (325 mg/d vs 81 mg/d) had no significant effect on the ARDS incidence (25% vs 27%, respectively; $P = .77$).[19] In addition, there was no marked difference in ARDS prevalence between subjects who continued and subjects who discontinued aspirin usage during an ICU stay (22% vs 31%, respectively; $P = .08$) as well as among subjects who continued to receive in-hospital aspirin for 1, 2, and 3 days (29.4%, 37%, and 30.2%, respectively; $P = .28$).[19]

Discussion

ARDS could develop into a serious condition within 3 d in many patients at risk, and within 1 week in nearly all patients at risk. Thus, pre-hospital antiplatelet therapy may be preventive for ARDS. We found that pre-hospital antiplatelet therapy before insults was associated with a markedly decreased risk of ARDS. Platelet-neutrophil aggregation plays an important role in ARDS.[15] Clinical studies indicate the potential beneficial effects of antiplatelet agents in reducing ARDS-related injuries.[22,23] In our meta-analysis, we found that pre-hospital antiplatelet therapy was associated with a decreased risk of ARDS, but the mortality of subjects at high risk was unaffected. Antiplatelet therapy, such as aspirin, likely exerts its effects in resolving inflammation through a combination of antiplatelet and anti-inflammatory activities.

Platelets have been recognized as being actively involved in the pathogenesis of ARDS, mainly via immunomodulatory mechanisms.[12] In a study with a mouse model, platelet depletion has been shown to lower neutrophil recruitment and inflammation as well as to improve the survival rate of ARDS.[15] Likewise, a prospective analysis of subjects with ARDS reported that aspirin is associated with lowered risks of ICU mortality.[27] Both antiplatelet and anti-inflammatory properties of aspirin may contribute to the resolution of inflammation (which involves apoptosis of activated inflammatory cells) and the attenuation of lung injuries in ARDS.[28,29] Specifically, aspirin irreversibly inhibits cyclooxygenases (1 and 2), which prevents the formation of thromboxane A_2 (a mediator of platelet aggregation), and prostaglandin E_2 (a mediator of inflammation) from the membrane-derived arachidonic acid.[28]

RESPIRATORY CARE Paper in Press. Published on February 11, 2020 as DOI: 10.4187/respcare.07177

Decreased platelet aggregates due to thromboxane A_2 reduction can impede the recruitment of neutrophils to the alveolar space.[27] Aspirin-induced nitric oxide released from endothelial cells also lowers the migration and infiltration of leukocytes, thereby lessening inflammation.[30] Moreover, results of studies indicate that aspirin-triggered 15-epi-lipoxin A_4 elicits anti-inflammatory effects by promoting neutrophil apoptosis and inhibiting peroxynitrite production in vivo.[29,31] The suppression of peroxynitrite hinders pro-inflammatory nuclear factor kappa B activation and further alleviates the persistent inflammation in ARDS.[31] Interestingly, a low dose of aspirin (75 mg) has been shown to lessen the innate immune responses and prevent the accumulation of polymorphonuclear leukocytes and macrophages that are independent of nuclear factor kappa B regulation.[32]

Several human studies were performed to investigate the effects of antiplatelet therapy on ARDS, but conflicting results were found.[18-20,22-25] An RCT showed that administration of aspirin within 24 h of presenting to an emergency department did not reduce the risk of ARDS at 7 d.[16] Our meta-analysis results suggested that pre-hospital antiplatelet therapy has a significant negative association with the ARDS rate. Notably, studies included in the analysis were either cohorts or case-control investigations, and none were RCTs. Based on the demographics, the subjects who received antiplatelet therapy were older and had markedly greater comorbidities than the subjects without antiplatelet therapy.[19,22] For example, chronic kidney diseases, cardiovascular diseases, and diabetes were commonly present in the subjects who were taking aspirin.[19]

To minimize potential confounding variables related to baseline differences in pre-hospital antiplatelet therapy users and nonusers, a propensity score was used to determine the probabilities of receiving antiplatelet therapy in the pre-hospital setting. After adjusting for the propensity score (calculated from a multivariate logistic regression model with variables such as age and APACHE [Acute Physiology and Chronic Health Evaluation] II score), a reduced rate of ARDS was still observed in the subjects treated with pre-hospital antiplatelet agents.[18-20,22,23,25] With respect to mortality, there were no marked differences between subjects with and those without pre-hospital antiplatelet therapy. Death occurred not only in the population affected by ARDS but also in the subjects without ARDS, as shown in other studies.[18,22,23,25] Thus, due to comorbidities and differences in antiplatelet therapy, such nonsignificance between the groups could exist.

Although the majority of the studies did not report the duration of pre-hospital antiplatelet therapy, it was presumed that the subjects received antiplatelet therapy on a long-term basis because antiplatelet agents are commonly administered for chronic cardiovascular diseases. Clinical evidence shows a potential of pre-hospital antiplatelet therapy in preventing ARDS.[22,33] Interestingly, Mazzeffi et al[20] included subjects who received antiplatelet therapy 5 d before aortic valve replacement surgery. However, the potential therapeutic or preventive effect of antiplatelet therapy on the occurrence of ARDS in patients at high risk requires further elucidation.

Limitations of the current study included the lack of evidence investigation on whether different antiplatelet agents could affect morbidity and mortality with selected studies of those subjects taking aspirin or clopidogrel as the single antiplatelet agent. Because subject populations that used clopidogrel or other platelet inhibitors were limited and the association of clopidogrel and its outcomes were undetermined, there was no such evidence to show the differentiation between aspirin and clopidogrel in relation to ARDS, which requires further investigations.

Conclusions

Analysis of our data showed that pre-hospital antiplatelet therapy was associated with a decreased risk of ARDS. Thus, platelet-neutrophil aggregation plays a key role in ARDS. Yet, the mortality of the subjects at high risk was unaffected. Further clinical investigations, especially RCTs, are needed to elucidate the molecular role of pre-hospital antiplatelet therapy in ARDS. Whether this association is affected by the confounding effects of comorbidities, such as vascular diseases, may alter the duration and dose of antiplatelet therapy.

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