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Research Article

Improved Outcomes in Patients Hospitalised with Community Associated Pneumonia: Can Established Warfarin Therapy Play a Role?

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Abstract

Community-Acquired Pneumonia (CAP) remains a common and serious infection in all developed countries. CAP remains associated with significant mortality. It has been suggested that adjunctive therapy, given in combination with antimicrobials, may improve CAP treatment outcomes.

This observational study sought to identify factors associated with improved short-term outcome in adult patients hospitalised with radiologically-confirmed CAP in Malta. The influence of established warfarin treatment on outcome in this cohort of patients was also assessed.

We retrospectively studied patients with radiologically diagnosed CAP requiring admission to the only tertiary care hospital in Malta over between 2011 and 2013. Ethical clearance was obtained. The radiological diagnosis was validated by the investigators using the hospital Picture Archiving and Communication System (PACS) system. Eligible patients needed to be at least 16 years old.

Through logistic regression analysis, increased 30-day mortality was positively associated with increased CURB-65 scores between two and four, radiologically severe pneumonia, and increasing age. However, mortality was significantly reduced in patients taking warfarin on admission, independent of INR levels (OR 0.24, 95%CI: 0.11-0.52).

This seemingly protective effect of warfarin, hypothetically through its influence on disturbed thrombin formation and alveolar fibrin deposition, merits further investigation in larger populations.

Keywords: Anticoagulants; Community acquired pneumonia; Morbidity; Mortality

Abbreviations

CAP: Community Acquired Pneumonia; PACS: Picture Archiving and Communication System; CRP: C Reactive Protein; INR: International Normalized Ratio; OR: Odds Ratio; ALI: Acute Lung Injury

Introduction

Community-Acquired Pneumonia (CAP) remains a common and serious infection in terms of morbidity and mortality within developed countries [1]. Several factors have been shown to influence CAP outcomes [1,2]. Despite the improved literature base, CAP remains associated with significant mortality. In addition, there are still knowledge gaps in this field, particularly in the elderly population [1]. Oral anticoagulation is frequently prescribed for a number of medical conditions such as thrombo-embolic disease and cardiac arrhythmias, often found within the same patient population who develop CAP. There is however little information in the literature whether concurrent oral anticoagulant therapy impacts on CAP outcome. Based on these findings, we sought to identify those factors influencing CAP outcomes in our local cohort of patients, in particular those on established oral anticoagulant therapy.

It has been suggested that adjunctive therapy, given in combination with antimicrobials, may improve CAP treatment outcomes [3].

Anticoagulant therapy has proven to be a successful therapeutic adjunct in the treatment of patients with sepsis [4,5]. Pulmonary changes in thrombin formation in patients with pneumonia are remarkably similar to systemic changes in coagulation observed in septic patients [4,5]. The mechanisms that contribute to disturbed alveolar fibrin turnover are similar to those found in the intravascular spaces during severe systemic inflammation [5]. In addition, nebulised anticoagulants have been demonstrated to attenuate pulmonary coagulopathy as well as inflammation in acute lung injury [6].

Materials and Methods

We retrospectively studied patients with radiologically diagnosed CAP requiring admission to the only tertiary care hospital in Malta over between 2011 and 2013. Ethical clearance was obtained. The radiological diagnosis was validated by the investigators using from the hospital Picture Archiving and Communication System (PACS) system. Eligible patients needed to be at least 16 years old

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Table 1: Baseline characteristics for the total cohort of patients.

Baseline characteristics	n=211
Age (years)	
Mean (SD)	77 (12)
Median (range)	78 (17-99)
Gender n (%)	
Male	124 (58.8)
CURB Score n (%)	
0	22 (10.4)
1	51 (24.1)
2	88 (41.7)
3	35 (16.5)
4	14 (6.6)
5	1 (0.005)
Smoking history, n (%)	
Current smoker	39 (18.4)
Level of ward care, n (%)	
General medical ward	121 (57.3)
Cardiac monitor + SpO2 monitoring	61 (28.9)
Intensive care	29 (13.7)
Duration of hospitalization (days)	
Mean (SD)	9.9±7.5
Median (range)	8 (1-46)
Seasonality (%)	
Spring	23.7%
Summer	14.2%
Autumn	25.1%
Winter	36%
Co-morbidities n (%)	
diabetes	60 (28.4)
ischaemic heart disease	100 (47.4)
chronic lung disease	55 (26)
congestive heart failure	105 (49.8)
chronic kidney disease	13 (6)
chronic liver disease	6 (0.03)
immunosuppressed	17 (8)
Radiological findings n (%)	
lobar pneumonia	151 (71.6)
bilateral pneumonia	39 (18.5)
multilobar pneumonia	17 (8)
bronchopneumonia	4 (1.8)
Blood indices	
Mean urea (mmol/L)	11.2±7.1
Mean platelet count (/L)	235.3±97.9 x 10^9
Mean baseline CRP (mg/l)	130±112

and admitted to hospital with a radiologically-confirmed CAP. Outcome was recorded in terms of 30-day mortality following hospital admission. The case definition for CAP was the detection on admission of an acute illness with cough and at least one of: either new focal chest signs and/or fever for more than four days or dyspnoea/tachypnoea, and no other obvious cause which were supported by chest radiograph findings of lung shadowing deemed to be new [7]. Analyses were performed using Medcalc, version 12.5.0.0 (Medcalc Software, Mariakerke, Belgium). The prevalence of each possible factor studied was compared between the group alive at 30 days and those who had deceased in this time period. Independent t-test was used to compare platelet counts and CRP on admission while the Mann-Whitney was used for age, hospital days, urea and INR levels since these were non-parametric in distribution; Chi-squared test was used to compare proportions. A p-value of <0.05 was taken to be statistically significant. Factors showing p-values <0.05 were then extracted, introduced into a separate model and retested through stepwise logistic regression to establish a multivariate model of factors associated with 30 day mortality.

Results and Discussion

Our cohort included a total of 211 patients, who were admitted with radiologically confirmed CAP. Table 1 shows the baseline characteristics of the patients. A total of 134 complications were reported in this study group. Respiratory complications included respiratory failure (18.5%), sepsis (16%), pleural effusion (11%), empyema (1.4%) and lung abscess (0.5%). 34 complications were not respiratory-related. 66 patients (31%) died within thirty days of the event. When compared to group still alive after this period of time, deceased patients tended to be older, with CURB-65 scores of three or four and bilateral pneumonia, required intensive care and have previous underlying chronic lung disease (Table 2). Out of the 211 studied patients, 92 (43.6%) were on warfarin on admission for a variety of co-morbidities including atrial fibrillation, prosthetic valves, thromboembolic disease, peripheral vascular disease and anti-phospholipid syndrome. Patients on warfarin had a better mortality outcome (p=0.0001) whereas no difference in outcome was linked to INR levels on admission or treatment with statins/aspirin. Using stepwise logistic regression analysis, controlled for INR levels on admission and treatment with statins/aspirin, 30-day mortality was found to be significantly associated with CURB-65 scores of two, three and four together with radiologically severe pneumonia and increased age (Table 3). The reduced mortality in patients taking warfarin on admission, previously identified in univariate analysis, was confirmed in the regression model. Patient on warfarin at admission had more than a four-fold increased chance of survival compared with the controls (OR 0.24, 95%CI: 0.11-0.52). The pseudo-R2 for this model was 0.422.

Thirty-day mortality in our cohort of patients was 31% (66 of 211 patients); this was rather high when compared to international studies [1,8,9]. However, mortality rates exceeding 20% have been quoted [10,11]. This high mortality rate may be due to strict inclusion criteria with radiological confirmation and patients requiring hospital admission with higher CURB-65 scores and more severe, multiple co-morbidities.

In line with our findings, other studies have linked increasing age to worse CAP outcomes [7,8] probably because symptoms are less commonly reported by older patients [12,13], resulting in delay in

Table 2: Baseline characteristics for alive and deceased individuals.

Baseline characteristics	Dead (n=66)	Alive (n= 145)	*p*
Age (years)			
Median (IQR)	80 (75-87)	76 (71-83)	0.007
Gender (%)			
Female	25 (38)	63 (43.5)	NS
Male	41 (62)	82 (56.5)	NS
CURB Score n (%)			
0	5 (7.7)	17 (11.7)	NS
1	4 (6)	47 (32.4)	<0.001
2	25 (38)	63 (43.4)	NS
3	23 (35)	12 (8.3)	<0.001
4	9 (13.6)	5 (3.4)	0.006
5	0 (0)	1 (0.01)	NS
Smoking history, n (%)			
Current smoker	10 (15)	29 (20)	NS
Level of ward care, n (%)			
General medical ward	32 (48.4)	89 (61.4)	NS
Cardiac monitor + SpO_2 monitoring	14 (21.2)	47 (32.4)	NS
Intensive care	20 (30.3)	9 (6.2)	<0.001
Duration of hospitalization (days)			
Median (IQR)	6 (3-13)	8 (6-13)	0.02
Seasonality (%)			
Spring	16 (24.2)	34 (23.4)	NS
Summer	8 (12.1)	23 (15.8)	NS
Autumn	20 (30.3)	34 (23.4)	NS
Winter	22 (33.3)	54 (37.2)	NS
Co-morbidities n (%)			
Diabetes	23 (34.8)	37 (25.5)	NS
Ischaemic heart disease	26 (39.4)	74 (51)	NS
Chronic lung disease	24 (36.4)	31 (21.4)	0.02
Congestive heart failure	28 (42.4)	77 (53.1)	NS
Chronic kidney disease	4 (6.1)	9 (6.2)	NS
Chronic liver disease	3 (4.5)	3 (2)	NS
Immunosuppression	7 (10.6)	9 (6.2)	NS
Radiological findings n (%)			
Lobar pneumonia	38 (57.6)	113 (77.9)	0.002
Bilateral pneumonia	19 (28.8)	20 (13.8)	0.009
Multilobar pneumonia	8 (12.1)	9 (6.2)	NS
Bronchopneumonia	1 (1.5)	3 (2)	NS
Radiologically severe pneumonia	27 (42.4)	29 (22.1)	0.006
Blood indices at time of admission			
Median urea (mmol/L)	13.1	8.1	<0.001
Mean platelet count (/L)	222±97.7	241±97.8	NS
Median INR on admission	1.13±0.3	1.34±0.8	NS
Mean baseline CRP (mg/l)	92±0	116±88	NS
Treatment at time of admission			
Antibiotics	13 (19.7)	33 (22.8)	NS
Warfarin	15 (22.7)	77 (53.1)	0.0001
Statins / Aspirin	25 (25.5)	37 (37.9)	NS

Table 3: Logistic regression analysis of factors which influenced CAP outcome.

Variable	Odds ratio	95% CI
Age	1.0344	1.0026 to 1.0672
CURB-65 Score 2	3.1029	1.2651 to 7.6104
CURB-65 Score 3	15.0217	5.1011 to 44.2361
CURB-65 Score 4	13.1895	3.0740 to 56.5916
Radiologically severe pneumonia	2.7596	1.3071 to 5.8260
Patients on warfarin at admission	0.2431	0.1145 to 0.5160

diagnosis and treatment initiation. Several studies have also shown that mortality increased with increasing CURB-65 score [1,13,14], as has our study. Radiological severity was also associated with a worse outcome as was described in other studies [15,16]. However, the association of decreased mortality in patients on warfarin treatment is novel and potentially very interesting. Patients on warfarin clearly showed better mortality outcomes, irrespective of INR levels on admission or other treatments. Alveolar fibrin deposition is an important feature of Acute Lung Injury (ALI), ARDS and pulmonary infection. The mechanisms that contribute to disturbed alveolar fibrin turnover are localized tissue factor-mediated thrombin generation and depression of bronchoalveolar urokinase plasminogen activator-mediated fibrinolysis, caused by the increase of plasminogen activator inhibitors. These effects on pulmonary coagulation and fibrinolysis are regulated by various pro-inflammatory cytokines and are similar to those found in the intravascular spaces during severe systemic inflammation [4]. Based on the fact that inflammation not only leads to dysregulation of the coagulation system, but also activation of coagulation amplifiers in the inflammatory processes, it could be questioned whether the apparent advantage of anticoagulant therapy in CAP could be related to its influence on disturbed thrombin formation [4]. In Malta, warfarin is the most commonly prescribed oral anticoagulant used in the long term. Our study has shown improved 30-day mortality following a CAP in patients receiving warfarin. One must keep in mind the delayed onset of action of warfarin, if it were to be used in the acute setting.

Strengths and Limitations

The limited sample size of patients on oral anticoagulants was a limiting factor in our study, together with the fact that patients were recruited from a single country. However, our cohort is representative of the whole population since Mater Dei Hospital is the main hospital in Malta. An additional limitation is that we did not use severity scores like the PSI to determine factors which influence mortality. Our study was limited to patients on established anticoagulation with warfarin. Hence we are unable to compare results with other novel anticoagulants.

Conclusion

It should be pointed out that the study involved a limited sample size from a single country, although the local circumstances make it representative of the whole population. Severity scores like PSI were not utilised. In addition, our study was limited to patients on established anticoagulation with warfarin and not other anticoagulants. Nevertheless the finding that hospitalised CAP patients on established home warfarin treatment had less

complications and decreased 30-day mortality is one that merits further investigation to establish whether these results are replicated in other centres and if they may be extrapolated to alternative faster acting novel anticoagulants.

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