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Decreased Hospital Length of Stay With Early Administration of Oseltamivir in Patients Hospitalized With Influenza

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Abstract

Objective: To evaluate the effects of timely oseltamivir administration in patients hospitalized with seasonal influenza.

Patients and Methods: We performed a single-center retrospective cohort study for hospitalized patients who tested positive for influenza between December 1, 2010, and July 1, 2014. We compared outcomes for patients who received antivirals within 48 hours of symptoms to those of patients who either received oseltamivir after 48 hours or never received oseltamivir. Hospital length of stay (LOS) and 90-day mortality were compared using Cox regression models. Antiviral administration was analyzed as a time-varying covariate.

Results: During the study period, 433 patients were hospitalized with laboratory-confirmed influenza. Of these patients, 146 (33.7%) received oseltamivir within 48 hours of symptoms, 202 (46.7%) received oseltamivir after 48 hours of symptoms, and 85 (19.6%) did not receive antivirals. Baseline characteristics were similar among these patient groups. Receiving oseltamivir within 48 hours was associated with shorter hospital LOS (5.9 days vs 7.2 days; P=.03) but no significant difference in 90-day mortality (13.7% vs 11.5%; P=.51). In a Cox regression analysis, patients who received antivirals within 48 hours had a 50% higher chance of being discharged (hazard ratio, 1.50; 95% CI, 1.14-1.98) on any given day during hospital stay.

Conclusion: In patients hospitalized with laboratory-confirmed influenza, timely administration of oseltamivir was associated with shorter hospital LOS.

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Seasonal influenza is an acute viral respiratory illness associated with significant morbidity, mortality, and health care utilization.[1] The burden of influenza is extensive, with an estimated total economic burden estimated to be more than $87 billion in both direct and indirect medical costs. Annually, it is estimated that there over 200,000 hospitalizations due to influenza[2] with over 3 million annual days of hospitalization.[3] The World Health Organization estimates that there are 3 to 5 million annual cases of influenza worldwide leading to an estimated 500,000 deaths,[4] while in the United States, it is estimated that influenza leads to approximately 1.4 to 16.7 deaths per 100,000 persons annually.[5]

Although influenza is a self-limited infection in most individuals, it is associated with increased morbidity and mortality in high-risk populations. Those at highest risk include the elderly, immunocompromised patients, and those with comorbid medical conditions. Beyond supportive measures and treating secondary bacterial infections, the mainstay of influenza treatment is with antiviral medications. Neuraminidase inhibitors (NAIs) are approved by the US Food and Drug Administration for use against influenza.[6] Neuraminidase inhibitors inhibit the activity of viral neuraminidase, inhibiting viral replication. The NAIs have been studied extensively in the outpatient setting, and

several randomized controlled trials have found that the duration of influenza infection in healthy patients can be shortened if NAIs are used within 48 hours of symptom onset.[7-9] However, the benefits of NAIs in reducing outcomes such as development of pneumonia, duration of hospitalization, and death is less established. Although some systematic reviews have found a mortality benefit with use of oseltamivir in hospitalized patients,[10] other large systematic reviews have reported that oseltamivir does not reduce rates of hospitalization.[11] Given the extensive burden of influenza, further investigation is needed to help determine what benefits NAI therapy may have in hospitalized patients. Additionally, the timing of antiviral administration remains an area in need of further research because there are conflicting data on whether antiviral use within 48 hours of symptom onset has benefit in patients hospitalized with influenza. Our objective in this study was to analyze whether timely oseltamivir administration in patients hospitalized with influenza resulted in any differences in mortality or other patient-important outcomes.

PATIENTS AND METHODS

We conducted an observational single-center retrospective cohort study. The study was approved by the Mayo Clinic Institutional Review Board (Rochester, Minnesota) before initiation. The requirement for written informed consent was waived by the institutional review. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used in the conduct of this study as well as in the reporting of our results.[12]

Study Population

The study population consisted of consecutive adult (aged ≥18 years) patients admitted to Mayo Clinic Saint Marys Hospital and Mayo Clinic Methodist Hospital between December 1, 2010, and July 1, 2014. All patients were required to have a single nasopharyngeal polymerase chain reaction (PCR) test positive for influenza A or influenza B. Patients were excluded if they declined the use of their medical records for research purposes.

Predictor Variable: Oseltamivir Administration

The primary predictor variable was timely oseltamivir administration, defined as medication administration within 48 hours of symptom onset as recommended by the Centers for Disease Control and Prevention.[1] The results were compared to those in a cohort of patients who either received delayed oseltamivir (after 48 hours) or never received oseltamivir at all. Timing of the symptom onset was determined by retrospective medical record review conducted by one of the study investigators (L.D.).

Outcome Variables

The primary outcome was mortality 90 days after hospitalization. Secondary outcomes were hospital length of stay (LOS), intensive care unit (ICU) LOS, development of acute kidney injury, and development of acute respiratory distress syndrome. For the primary and secondary outcomes, patients who received oseltamivir within 48 hours were compared with the cohort of patients who received antivirals after 48 hours or did not receive them at all. Additionally, a Cox regression analysis was performed comparing hospital LOS and 90-day mortality in patients who received oseltamivir within 48 hours compared with those who received oseltamivir after 48 hours, with no antiviral administration used as a comparator.

Data Collection

Baseline characteristics were collected for all patients, including sex, age, timing of symptom onset, medication administration, and assessment of chronic health conditions via Charlson Comorbidity Index and Sequential Organ Function Assessment scores. Influenza cases were identified using an institutional database query tool (database discovery and query builder). Data retrieval was performed with the help of a comprehensive institutional clinical research database (Advanced Cohort Explorer), as well as institutional Microsoft SQL—based databases that retrieve variables for all ICU patients in near real time (the ICU data mart and OR data mart). We have previously validated these data extraction techniques against manual data extraction.[13-16] Most of the variables were obtained using the validated search strategies described

TABLE 1. Baseline Demographic Characteristics of the Study Cohort[a,b]

Variable	No antivirals within 48 h of symptoms (N=287)	Antivirals within 48 h of symptoms (N=146)	*P* value
Sex			.27[c]
Male	149 (51.9)	84 (57.5)	
Female	138 (48.1)	62 (42.5)	
Age (y)	68.6±17.7	66.4±18.4	.22[d]
Race, white	251 (87.5)	134 (91.8)	.14[c]
Charlson Comorbidity Index score	6.0±3.3	5.7±3.6	.55[d]
Current smoker	30 (10.5)	15 (10.3)	.95[c]
Asthma	55 (19.2)	35 (24.0)	.24[c]
COPD	76 (26.5)	40 (27.4)	.83[c]
Heart failure	41 (14.3)	20 (13.7)	.87[c]
Chronic kidney disease	78 (27.2)	28 (19.2)	.07[c]
Diabetes	79 (27.5)	40 (27.4)	.98[c]
Active malignancy	62 (21.6)	34 (23.3)	.69[c]

[a]COPD = chronic obstructive pulmonary disease.
[b]Data are presented as No. (percentage) of patients or mean ± SD.
[c]χ^2 test.
[d]*t* test.

previously. For variables lacking validated automated extraction techniques, manual medical record review was performed. Timing of symptom onset was determined via manual medical record review. All data were extracted by a researcher trained in the use of these databases.

Statistical Analyses

Epidemiological data were collected, with categorical variables summarized as frequency (percentage). Continuous variables were expressed as mean ± SD or median with interquartile range (IQR) as appropriate. When comparing patient groups, categorical variables were compared using χ^2 tests or Fisher exact test, as appropriate. Continuous variables were compared using *t* tests for normally distributed data or Wilcoxon analysis for nonnormally distributed data. As an additional sensitivity analysis, hospital LOS and 90-day mortality were compared using Cox regression models. For this step, we analyzed antiviral administration as a time-varying covariate. For LOS, patients who died in the hospital were censored on the day of death. All analyses were adjusted for age, sex, and comorbidities. In all final analyses, statistical significance was considered present when the hypothesis test value was less than *P*=.05. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute).

RESULTS

Between December 1, 2010, and July 1, 2014, 433 patients were admitted to Mayo Clinic hospitals in Rochester, Minnesota, with laboratory-confirmed influenza. Of these 433 patients, 146 (33.7%) received antivirals within 48 hours of symptom onset, while 202 (46.7%) received antivirals after 48 hours of symptom onset and 85 (19.6%) did not receive any antivirals.

Baseline characteristics such as sex, age, smoking status, comorbid medical conditions, and an assessment of chronic health comorbidities via Charlson Comorbidity Index and acuity of illness on presentation via Sequential Organ Function Assessment score are reported in Table 1. There were no major differences in the cohort with regard to these baseline characteristics.

In those who received antiviral therapy, the median time from symptom onset to initiation of antiviral therapy was 3.4 days (IQR, 2.1-5.7 days) across the cohort (early cohort: 1.6 days [IQR, 1.2-1.8 days]; delayed cohort: 4.2 days [IQR, 3.0-6.4 days]). The

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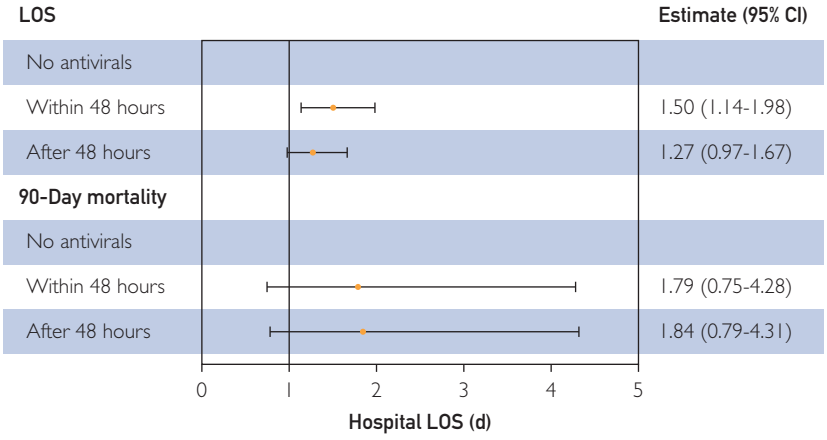

FIGURE. Hazard ratio for hospital discharge was 1.50 (interquartile range, 1.14-1.98) on any given day of hospitalization for patients who received antivirals within 48 hours compared with those who did not. Hazard ratio for 90-day mortality was 1.79 (0.75-4.28) for patients receiving antivirals within 48 hours compared with those who did not. LOS = length of stay.

median time from hospital presentation to initiation of antiviral therapy was 1.3 days (IQR, 0.7-1.8 days) across the cohort (early cohort: 0.9 days [IQR, 0.6-1.7 days]; delayed cohort: 1.3 days [IQR, 0.8-1.8 days]; *P*=.04). The median time to obtaining a positive influenza PCR result from the time of hospital presentation was 1.1 days (IQR, 0.7-1.6 days) across the cohort (early cohort: 0.8 days [IQR, 0.6-1.6 days]; delayed cohort: 1.3 days [IQR, 0.8-1.7 days]; *P*=.003).

There were 53 deaths within 90 days of hospital admission in our study. Of these deaths, 20 (37.7%) were patients who received oseltamivir within 48 hours of symptom onset, whereas 33 (62.3%) were patients who either received oseltamivir late or did not receive oseltamivir at all. In the Cox regression analysis, there was no statistically significant difference in mortality between those receiving early oseltamivir vs those who received late oseltamivir or did not receive oseltamivir at all (hazard ratio [HR], 1.79; *P*=.19; Figure).

Patient outcomes are outlined in Table 2. The median hospital LOS for the entire cohort was 5.6 days (IQR, 2-6 days). Early oseltamivir administration was associated with faster time

TABLE 2. Patient Outcomes[a,b]

Variable	No antivirals within 48 h of symptoms (N=287)	Antivirals within 48 h of symptoms (N=146)	*P* value
SOFA score within 24 h of hospital admission	2.5±2.8	2.8±2.6	.31[c]
Hospital length of stay (d)	7.2 (4.5-13.7)	5.9 (2.9-6.7)	.03[c]
ICU length of stay (d)	2.2 (0.96-5.8)	1.5 (0.85-7.6)	.11[d]
Acute kidney injury	17 (5.9)	11 (7.5)	.90[d]
ARDS	18 (6.3)	5 (3.4)	.12[d]
90-Day mortality	33 (11.5)	20 (13.7)	.51[d]

[a]ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range; SOFA = Sequential Organ Failure Assessment.
[b]Data are presented as mean ± SD, median (IQR), or No. (percentage) of patients.
[c]*t* test.
[d]χ^2 test.

to hospital discharge. The median LOS for the early oseltamivir cohort was 5.9 days, compared with 7.2 days for those who either received oseltamivir after 48-hours or did not receive oseltamivir at all (P=.03). In Cox regression analysis, on any given day during hospitalization, a patient who received antivirals within 48 hours had a 50% higher chance of being discharged (HR,1.50; 95% CI, 1.14-1.98) compared with a patient who did not receive antivirals on the same day (Figure). There was no significant difference in hospital LOS between those who received oseltamivir after 48 hours and those who did not receive any antiviral medications (HR, 1.27; 95% CI, 0.97-1.67). There was no difference in ICU LOS, development of acute kidney injury, or acute respiratory distress syndrome among the 3 groups.

DISCUSSION

In this study, we aimed to determine how administration of oseltamivir in patients hospitalized with influenza affected patient-important outcomes such as mortality, ICU LOS, and hospital LOS. The primary finding of our study was that use of oseltamivir in hospitalized patients did not change mortality at 90 days but did result in substantially decreased hospital LOS. Although most of the delay between symptom onset and antiviral administration was due to delayed presentation to the hospital, there were additional delays in obtaining influenza viral testing and administering antiviral therapy in the hospital.

The impact of seasonal influenza is substantial, with over 200,000 hospitalizations annually in the United States.[2] Our results support the growing consensus that oseltamivir improves patient-important outcomes in those hospitalized with influenza. The benefit of oseltamivir in reducing symptom duration in adults with seasonal influenza has been established previously by several high-quality studies.[7,8,11,17-19] These studies were predominantly conducted in the outpatient setting, and there are limited data regarding the role of oseltamivir in hospitalized patients. McGeer et al[20] found in an observational study that hospitalized patients with influenza treated with oseltamivir had a reduction in mortality compared with patients who did not receive treatment. In an observational study, Lee et al[21] found that timely administration of oseltamivir was associated with earlier hospital discharge as well as decreased mortality. A reduction in mortality was also seen in a retrospective study done in 12 countries during the outbreak of H5N1.[22] Furthermore, Chaves et al[23] conducted a retrospective study of 3 influenza seasons with over 6500 elderly patients who were hospitalized with influenza enrolled. This study found that oseltamivir was associated with shorter hospital LOS in addition to a decreased need for placement in a rehabilitation facility after hospital discharge. Domínguez-Cherit et al[24] reported reduced mortality with NAI therapy in critically ill patients with influenza. Further evidence for the benefit of NAI therapy was seen in a systematic review of 74 observational studies that found that the use of NAI therapy in high-risk patients hospitalized with influenza was associated with decreased mortality, shorter hospital LOS, and shorter duration of influenza symptoms.[25] Another systematic review of patients hospitalized with influenza during the 2009 H1N1 influenza pandemic included 78 studies with over 29,000 patients. Muthuri et al[10] found that NAI therapy decreased both hospital LOS and mortality. The results of the numerous observational studies and systematic reviews suggest that NAI therapy improves outcomes in patients hospitalized with influenza, although the extent of the benefit remains unclear. Our results indicate that NAI use leads to decreased hospital LOS; however, we have not observed a mortality benefit.

The timing of antiviral administration in patients hospitalized with influenza is also an area of dispute. Randomized controlled trials of NAIs in outpatients with mild illness revealed reduction of symptom duration when used within 48 hours, and little to no benefit was seen when used more than 2 days after symptom onset.[1,7,8] However, the use of NAIs after 48 hours in hospitalized patients has had mixed results. One study found that treatment with oseltamivir was associated with a reduction in mortality, regardless of the timing between symptom onset and antiviral administration.[26] Other studies have found that early administration of antiviral therapy was most beneficial, but benefits were still

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seen when therapy was initiated more than 48 hours after symptom onset.[10,21-23] In one retrospective study, NAIs had a mortality benefit that was most pronounced within 2 days of symptom onset; however, a mortality benefit was still seen up to 5 to 6 days after symptom onset.[22] Muthuri et al[27] performed a systematic review of patients hospitalized with influenza and found that NAI therapy administered at any time was not associated with reduced mortality, while a reduction in mortality was seen when NAI therapy was initiated within 48 hours of symptom onset. This study had considerable heterogeneity between the studies, which may limit its generalizability. The H1N1 pandemic in 2009 led to numerous studies regarding the use of NAIs in hospitalized patients with influenza. A systematic review of 78 studies from this pandemic found that NAI use was associated with reduced mortality, regardless of the timing of antiviral administration. A larger reduction in mortality was seen when antivirals were administered within 48 hours of symptom onset, and each day of delayed treatment led to an increase in the HR for death.[10] We found that administration of oseltamivir within 2 days of symptom onset was associated with earlier hospital discharge. A nonsignificant trend toward earlier hospital discharge was noted when antivirals were administered after 2 days of influenza symptoms.

Our study has several strengths. First, this study was performed over a 4-year period, which allows for assessment of the effect of oseltamivir over different influenza seasons with varying influenza vaccine efficacy. Our patient cohorts were also well matched regarding baseline characteristics, comorbid medical conditions, and severity of illness. Oseltamivir was used as the drug of choice for influenza at the institution in this study, which allowed us to assess the effect of one drug on patients hospitalized with influenza, as opposed to having to study the effects of multiple NAIs. Finally, rapidly available PCR testing for influenza at our institution allowed for accurate diagnosis and treatment.

Our study also has notable limitations. First, the retrospective and observational nature of our analysis allows for the possibility of confounding. We attempted to mitigate this factor by ensuring that our cohorts were similar with regard to baseline characteristics, but the possibility of residual confounding remains. Given that our study population included only 433 patients, the small sample size may be underpowered to determine the effects of antiviral administration on mortality. Moreover, the small study population precluded the possibility of a 3-arm study design (timely antiviral administration, delayed antiviral administration, no antiviral administration). The data presented justify performance of a larger, multicenter study. Because of the retrospective nature of the study, the timing of symptom onset from influenza was determined by manual medical record review. Although checks were performed to ensure the accuracy of these data, prospective data collection would allow for more accurate assessment of symptom onset. Finally, this is a single-center study, which may limit generalizability of our findings.

CONCLUSION

Patients who received oseltamivir within 48 hours of symptom onset had a faster time to hospital discharge than patients who did not receive antivirals within 48 hours of symptom onset. Oseltamivir administration had no impact on 90-day mortality or other patient-important outcomes.

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Drs Dou and Reynolds contributed equally to this work.

Abbreviations and Acronyms: **HR** = hazard ratio; **ICU** = intensive care unit; **IQR** = interquartile range; **LOS** = length of stay; **NAI** = neuraminidase inhibitor; **PCR** = polymerase chain reaction

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