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Research Article

Correlation of days of illness on which oseltamivir was started with outcome in swine flu patients, in Government Medical College, Aurangabad (Jan-2015 to May 2015)

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ABSTRACT

Background: Since 2009, Government Medical College, Aurangabad, a tertiary care hospital in the Marathwada region of Maharashtra, India, has been regularly admitting cases of pneumonia and ARDS, that are labeled as swine flu suspects. Oseltamivir is effective in swine flu cases if given within 48 hours and better, within 24 hours of start of illness. However most of our patients do not get oseltamivir within 48 hours. Hence we decided to compare the outcome in patients who received oseltamivir within 48 hours and after that.
Methods: This is an observational, cross-sectional study comparing the time lag between the start of symptoms and getting the first dose of oseltamivir. 59 H1N1 positive patients were admitted to the swine flu ward between January to May 2015. We compared the two groups, one that received oseltamivir within 48 hours of start of symptoms and one that received after 48 hours and compared it with the outcome, i. e survival or death.
Results: 38 patients (64.40%) in our study belonged to the age group of 31-50. Out of 59 positive patients, only 7 received oseltamivir within 48 hours, of whom 4 died. 52 received oseltamivir after 48 hours of whom 20 died. All the 11 who were given non-invasive ventilation, whereas only 1 of the 25 on invasive ventilation survived.
Conclusions: Oseltamavir does not appear to have made a difference for survival whether it was given within 48 hours as compared to after 48 hours of onset of symptoms. However, these two groups were not comparable.

Keywords: Oseltamivir, Survival in swine flu, Oseltamivir given within 48 hours

INTRODUCTION

Department of Medicine, Government Medical College, Aurangabad, (which is a tertiary care hospital in the region), has been regularly admitting cases of pneumonia and ARDS, that are labeled as swine flu suspects in the Isolation Ward since 2009. Their throat swab is sent to National Institute of Virology (NIV) Pune and treatment is started immediately in the form of oseltamivir, respiratory support (as needed) and antibiotics. This year, from the 21st of Jan 2015 to the 10th of May 2015, we had 152 suspected swine flu admissions, of whom 59 were positive. Of these, 35 survived and 24 died. Since very few private hospitals in the city or neighborhood admit swine flu cases and of these, even fewer admit serious cases, the apparent mortality (40.67%) is high.

Another reason for this apparent high mortality is that, this year, we had instructions from the NIV (National Institute of Virology, Pune, Maharashtra) to send throat swabs for RT-PCR of only Category C patients as per the ministry of health family welfare guidelines[1] or having

high risk factors like pregnancy, diabetes or HIV infection. Hence though we treated all 152 suspected cases admitted to the ward as cases of H1N1, throat swab was examine by PCR of only 106 patients of whom only 59 came positive and 47 came negative. We could not test the milder cases though may have been cases of swine flu and they may have been wrongly labelled as negative because they were not tested.

METHODS

152 suspected H1N1 patients were admitted to the swine flu isolation ward of GMC, Aurangabad between January to May 2015. Detail history of duration of illness before receiving oseltamivir, risk factors, number of doctors visited before presenting to us was taken. Pulse, BP, respiratory rate, single breath count, SpO_2, state of hydration were recorded. Investigations done were hemogram, ABG, throat swab for H1N1 by RT-PCR, blood sugar, liver and kidney functions, portable X-ray of the chest and HIV status (after counseling). Treatment was started immediately without waiting for report in the form of oseltamivir, respiratory support and antibiotics. The 59, who reported positive for H1N1 were included in the study. The H1N1 negative ones were excluded from the study though they were given the full course of oseltamivir. The 59 positive patients who were positive for H1N1 by RT-PCR were divided in two groups, one group that had received the first dose of oseltamivir within 48 hours of illness and the other that had received after 48 hours. Statistical test of significance was applied with Yates correction.

RESULTS

As shown in Figure 1, most of the patients (64.40%) in our study belonged to the age group of 31-50. In our study males (32 i.e. 54.23%) were more as compared to females (27 i.e. 45.77%). The youngest patient was 10 months old and oldest was 75 years of age.

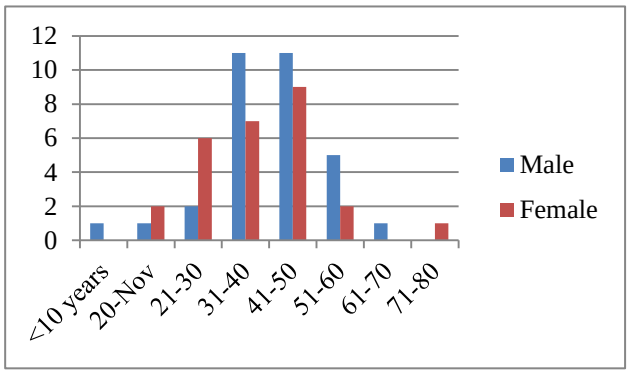

Figure 1: Age and sex distribution of swine flu patients.

As shown in Table 1, 14 patients were obese (waist-hip ratio criteria). 11 patients were hypertensive followed by 7 diabetes mellitus.

Table 1: Number of swine flu patients with co-morbidities.

Comorbidity	Survival	Death	Total
Obesity	3	4	7
DM + Obesity	2	1	3
DM + HTN + Obesity	2	2	4
HTN	2	3	5
RHD with MS	2	1	3
Pregnancy	1	2	3
Nephrotic syndrome	1	1	2
Hypothyroidism	1	0	1
HIV positive	1	1	2
Old PUL. TB	1	0	1
Old stroke	1	0	1
Rheumatoid arthritis	0	1	1
No comorbidity	22	12	34

*DM-Diabetes, HTN-Hypertension, RHD-Rheumatic heart disease, MS-Mitral stenosis, TB-Tuberculosis

Table 2 shows survivals and deaths of swine flu patients in whom oseltamivir was started either within or after 48 hours of illness. Out of 59 positive patients, only 7 received oseltamivir within 48 hours, of whom 4 died and 52 received oseltamivir after 48 hours of whom 20 died.

Table 2: Days of illness on which oseltamivir administered.

Days of illness	Survivals	Deaths	Total
≤2	3	4	7
>2	32	20	52
Total	35	24	59

As the two groups were not comparable, Chi-square test with Yates correction was applied.

Chi square equals 0.286 with 1 degree of freedom. The two-tailed P value equals 0.5928. The association between rows (groups) and columns (outcomes) is considered to be not statistically significant at 95% confidence levels).

This suggests that whether oseltamivir was started within 48 hours of start of symptoms or later, did not make a difference on the survival and mortality. However, the two groups are not comparable in terms of the sample size, as the number of patients who received oseltamivir within 48 hours is only 7 (11.84%) as compared to the 52 (88.16%) who received it after 48 hours, hence the results can be interpreted with 95 % confidence only.

Table 3 shows comparison of survivors who had risk factors, in groups that received oseltamavir within or after 48 hours. Of the total 35 survivors 11 had risk factors and 24 did not have any risk factor.

Table 3: Comparison of survivors who had risk factors, in groups that received oseltamavir within or after 48 hours.

Day of illness before receiving oseltamivir	With risk factors	Without risk factors	Total
≤2	1	2	3
>2	10	22	32
Total	11	24	35

Chi-square with Yates correction was applied. Chi square equals 0.006 with 1 degree of freedom. The two-tailed P value equals 0.9408. The association between rows (groups) and columns (outcomes) is considered to be not statistically significant).

It appears that in high risk patients, whether oseltamivir was given within 48 hours or after 48 hours of start of illness does not a make a difference for survival. However, in this observation also, the two groups are not comparable, the number in the first group (within 48 hours) being only 3, whereas that in the second group (after 48 hours) is 32. Also, the first group is so small that we ideally cannot apply statistical tests. Hence the result cannot be considered to be absolutely correct.

Table 4 shows mortality in patients with or without risk factors. Of the 24 patients who died, 12 had risk factors and 12 were without a risk factor.

Table 4: Mortality in patients with or without risk factors.

Day of illness after which oseltamavir was started	With risk factors	Without risk factors	Total
≤2	1	2	3
>2	11	10	21
Total	12	12	24

Chi-square with Yates correction, Chi square equals 0.381 with 1 degree of freedom. The two-tailed P value equals 0.5371.The association between rows (groups) and columns (outcomes) are considered to be not statistically significant).

Again, the two groups are not comparable as patients in the group that received oseltamivir within 48 hours are only 3 (12.5%) as compared to the high risk group that received it after 48 hours, i.e. 21 (87.5%).

DISCUSSION

Oseltamavir phosphate is an oral medicine, approved by the FDA in October 1999, for treating and preventing influenza.[2] It is a potent selective inhibitor of influenza A and B virus neuraminidases.[3] Influenza neuraminidase cleaves terminal sialic acid residues and destroys the receptor recognised by viral hemagglutinin, which are present on the cell surface, in progeny virions and in respiratory secretions. This enzymatic action of neuraminidase is essential for the release of virus from cells and enabling their spread to neighbouring healthy cells. Its concentration in lung has been reported to be as high as 5 times those of corresponding plasma levels.[4] Inhibition of neuraminidase activity leads to viral aggregation at the cell surface and reduced virus spread within the respiratory tract.

Seasonal influenza A has become worldwide resistant to Oseltamivir.[3] However, novel H1N1 (nH1N1 or swine influenza) remains susceptible to oseltamivir.[5,6] The incubation period of swine flu is 18 to 72 hours depending on the size of inoculums (H), but viral shedding may occur up to 24 hours before symptom onset and continues for five to 10 days.[7,8] Influenza is typically uncomplicated and self-limited in otherwise healthy patients. However, severe complications, such as pneumonia, encephalitis, respiratory failure, multi-organ failure, and death, can occur.[9]

Oseltamivir is said to be effective if given within 48 hours[10] and better, within 24 hours of the start of symptoms and have been shown to reduce the duration of fever and illness by 1- 2.5 days.[11] It can be safely given for 3 to 6 weeks. In immune-compromised patients, it may be given for 12 weeks.

The recommended dose for adults is 75 mg twice a day for 5 days, which gives adequate blood levels. Some experts recommend 150 mg BD in severe cases.

In renal failure, it may be given the dose of 30 mg daily for 5 days.[10]

Oseltamivir is a highly bio-available in capsule and suspension formulations and after conversion to active metabolite in the liver distributes throughout the body, including upper and lower respiratory tract. The terminal plasma elimination half-life is 1.8 hours in healthy adults.[12]

It is reported that survival is significantly increased by timely oseltamivir in serious cases. It is generally well tolerated except for few cases who get nausea,[13] vomiting and diarrhoea. Our patients tolerated it well.

A 5 days course of oseltamavir reduces the duration of sign and symptoms of uncomplicated influenza by 1-1.5 days if treatment is started within 2 days of onset of illness and may be effective if started upto 5 days after onset of symptoms.[14] It is approved for treatment of uncomplicated illness caused by influenza infection in adult aged >18 years who have been symptomatic for no more than 2 days.[15] Neuraminidase inhibitors have modest effectiveness against symptoms of influenza in otherwise healthy adults.[16]

The therapeutic efficacy of antiviral compounds in influenza has been demonstrated primarily in studies of young adults with uncomplicated disease. The effectiveness of these drugs in treatment and prevention of complications of influenza is unclear. Pooled analyses of observational investigations and some efficacy studies have suggested that treatment with oseltamavir may reduce frequency of lower respiratory complications and hospitalizations. Therapy for primary influenza pneumonia is directed at maintaining oxygenation and is most appropriately undertaken in an intensive care unit with aggressive support as needed.[17]

We have attempted to study the effect of oseltamivir in preventing mortality in patients who received it within 48 hours of start of symptoms as compared to those who received it late. However, the two groups are not comparable as patients in the group that received oseltamivir within 48 hours are only 7 (11.86%) as compared to the 52 (88.14) in the group that received it after 48 hours. As this is an observational study in which we could not design the two groups as it was not in our hands to increase the number of patients in the first group i.e., who received oseltamivir within 48 hours.

It was found that even if oseltamivir is given early in the course of the illness (within 48 hours), it does not have a statistically significant effect in reducing mortality. But till an alternative is available, it will be unethical to say that oseltamivir is ineffective and need not be given. Clinically, we do observe that it seems to make a difference in the relatively less serious cases and prevents progression or reverts them, though we do not have statistical backing for this. Also, it seemed to have efficacy in preventing H1N1 infection among health care workers, who had not received vaccines in the earlier to the epidemics.

We did not get a single admission that had received oseltamivir within 48 hours. We feel that this may make a difference, because, in fulminant cases, the H1N1 infection is likely to spread very fast and even 48 hours may be too long to halt it.

Majority of these swine flu patients presented with rapid progression of hypoxemia and bilateral alveolar infiltrates on chest X-ray. Other respiratory presentations were exacerbations of asthma or COPD, exacerbations of other underlying disease like CCF and secondary bacterial pneumonia.[18]

Vaccine may be the best form of prevention when supported by personal protection, cough hygiene and most importantly, frequent hand washing.

We recommend an integrated approach to prevent H1N1 infection. It is necessary to step up awareness among health care persons regarding starting oseltamivir early, within 24 hours, especially in high risk cases.

To conclude, in our study

1) Oseltamavir does not appear to have made a difference for survival whether it was given within 48 hours as compared to after 48 hours of onset of symptoms. However, these two groups were not comparable.

2) There is no statistically significant difference in survival of swine flu positive patients with high risk factors like pregnancy, HIV positivity, diabetes, heart disease, whether Oseltamivir was given within 48 hours as compared to after 48 hours of onset of symptoms.

3) Our experience with patients shows that Oseltamivir definitely controls symptoms and seems to play a preventive role in contacts (like medical personnel working in the swine flu ward).

4) It appears that those swine flu positive patients who survived, did so because of less severity of disease at the time of admission, natural course of viral disease, intensive care of patients and some unknown factors.

5) Though all the eleven patients (100%) who only needed non-invasive ventilation survived, only one out of the twenty five patients (4%) who required invasive ventilation survived. This indicates that in fulminant cases, the best possible intensive care may not help to save the patients. This emphasises earliest possible intensive management and vigilant observation of course of illness in swine flu patients.

6) In spite of a lot of efforts taken by the Government to spread awareness, many doctors do not start oseltamivir at an early stage even when an epidemic is on. The patients also go from one doctor to another and by the time they reach a tertiary care hospital, they have on an average visited at least two other health care facilities. More efforts are needed in this direction as ideally oseltamivir acts best within 24 hours.

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