As many as 11 million people are estimated to require medical care for burns every year. It is a global public health problem with an estimated 4.8 fire-related deaths per 100,000 population and 300,000 deaths annually. The highest prevalence rates are observed in Southeast Asia region, Western Pacific region, Eastern Mediterranean region, and the lowest in the Americas. The fire-related burns mortality rates range from around 1 to 1.3 per 100,000 population in the high-income countries of America and Europe to 5.5 in Africa and > 8 in Southeast Asia (8.3 in India). The low- and middle-income countries, which generally suffer from poverty, overcrowding, illiteracy, and lack of infrastructure, account for more than 90% of all mortalities and half of these occur in the Southeast Asia region. In nonfatal cases, prolonged hospitalization, disfigurement, and disability, in addition to lost wages, emotional trauma, and erosion of family resources, contribute to the adverse impact. The Southeast Asia region is, again, the most affected, with maximum fire-related burns burden, in terms of days lost.

Current management of burns involves stabilizing the patient, controlling infection, and assisting in physiological recovery. This is achieved by the maintenance of airway and breathing, fluid resuscitation, maintenance of adequate nutrition, wound care, topical and systemic antibiotic therapy, tetanus prophylaxis, and skin grafting. Despite improvements in the early care of burns patients, systemic inflammatory response syndrome, severe sepsis, and multiple organ dysfunction syndrome remain major causes of morbidity and mortality. The inflammatory processes aid wound healing...
by recruiting leukocytes and macrophages at the site, but excess of these interfere with the healing process. The clinical challenge is the application of therapeutic intervention only when these responses become excessive.6

Multiple serine proteases act as intermediaries in the systemic inflammatory process; these include trypsin, thrombin, chymotrypsin, kallikrein, plasmin, neutrophil elastase, cathepsin, neutrophil protease-3, and coagulation factors IXa, Xa, XIa, and XIIa. These proteases have an important role in regulation of inflammation through inter- and intracellular signaling pathways. To counter the excessive effects of these enzymes, several protease inhibitors are produced by the liver in the presence of inflammation; these include acute phase reactants such as α1-antitrypsin and proteins of the inter-alpha-inhibitor (IaI) family.7–9

Ulinastatin is a serine protease inhibitor, belonging to the IaI family, which is available since 1985 and is currently approved in Japan, China, South Korea, and India for a variety of indications like sepsis, acute pancreatitis, and acute circulatory failure due to hemorrhagic, bacterial, or traumatic shock. Ulinastatin was approved in India for use in the management of severe sepsis in 2012 and for acute pancreatitis in 2014. Significant decrease in the production of inflammatory mediators, oxygen-free radicals, and protective effect on the functions of multiple organs with reduced fluid requirements, through inhibition of lipid peroxidation, has been reported with the use of ulinastatin in animal models of burns.10–16 Multiple clinical studies have also reported significant decrease in inflammatory mediators, edema, and wound size with protective effect on multiple organ functions as well as decrease in mortality in patients with severe burns and severe burns–induced sepsis.14–16

This retrospective comparative case note review analysis aimed to study the impact of ulinastatin on the management of hospitalized patients with burn injury with special emphasis on mortality and hospital length of stay (LOS).

MATERIALS AND METHODS

Study Centre

This study was performed in the Department of Burns and Plastic Surgery, Eric Kharas Memorial Burns Centre, Masina Hospital, a 280-bedded multispecialty tertiary care hospital, located in the heart of Mumbai, the industrial and financial hub of India, with a population of 12 million people. Approval for the study was obtained from the director of the hospital.

Study Design

This is a retrospective, case note review analysis of patients from two periods—before and after introduction of ulinastatin in the management of hospitalized burns patients at Eric Kharas Memorial Burns Centre, Masina hospital. The patients from these two periods were divided into two groups and compared for outcomes.

Patients

All patients with acute burns admitted to the burns and plastic surgery department who received ulinastatin were identified. All such patients irrespective of age, gender, and extent or severity of burn injury and who either died or completed the in-patient treatment were included in the study. This comprised patients admitted from October 05, 2012, to April 27, 2015, and formed the ulinastatin group. For comparison, a cohort of similar number of patients admitted before the introduction of ulinastatin was identified and included in the control group. This group comprised patients admitted between February 01, 2011, and October 05, 2012.

Study Intervention

Patients in the ulinastatin group had received ulinastatin as intravenous infusion, for as many days as deemed necessary by the caring physician, in addition to the standard care as per hospital protocol. Ulinastatin was stopped based on clinical improvement and normalization of laboratory parameters, indicating improvement in organ functions.

Standard Care

Both groups had received all the standard care according to hospital protocol, and the aspects of patient management have not changed between the two periods. The supportive care included analgesics, intravenous fluids, packed red blood cells, fresh frozen plasma, albumin, and others, as indicated. All patients admitted for acute burns were given fluid resuscitation using Parkland formula with crystalloids, usually Ringer’s lactate solution. The wounds were cleansed with disinfectants and normal saline. Swabs from the burn wound were obtained and sent for microbial culture and antibiotic sensitivity testing. Topical antibiotics and wound dressings were applied in layers. Antitetanus immunoprophylaxis was provided as required. Prophylactic antibiotics (most commonly a third generation cephalosporin) were administered to all patients, while analgesics were given as required. This was followed by specific antibiotics based on culture and sensitivity tests performed on blood, wound,
and/or other specimens. Interventions for maintaining organ system functions—assisted ventilation, vasoressor support, and/or dialysis—were instituted as required. Other intensive care and surgical interventions were provided on a case-to-case basis in coordination with the intensive care and anesthetic team.

Data

Basic patient material was identified from the medical records of the hospital. Data were obtained on a predesigned case record form from the archived patients’ files. Data on patient demographics, burn details, major interventions, medications including antibiotics, blood and blood components, and I.V. fluids and outcomes including hospital LOS, intensive care unit (ICU) stay, and in-hospital mortality were extracted from the archived patients’ files. Additionally, vital parameters and available laboratory values—serum chemistry, hematology, electrolyte values on days 0 (day of admission), 3, 6, 9, and so on, and significant laboratory, culture, or imaging findings—were recorded. In the ulinastatin group, details of ulinastatin use, including the start date, duration, and total dose, were also recorded.

Outcomes

Outcomes of interest were in-hospital mortality and LOS in hospital and ICU. These outcomes were compared in the two treatment groups. Additionally, the outcomes were compared after stratifying the treatment groups based on the burnt BSA into following strata—BSA < 40%, BSA = 40 to 80%, and BSA > 80%.

Statistical Analysis

Data were collated in a Microsoft® (Microsoft Corporation, U.S.) Excel® spreadsheet and statistical analysis was performed using SAS® software version 9.4 (‘SAS Institute, U.S.’). The demographic and baseline characteristics have been summarized by treatment groups using descriptive statistics (number of patients [n], mean, SD, median) and were compared using either Pearson’s χ² test or Mann–Whitney U test, as appropriate. Mortality data have been summarized using frequency counts (n) and percentages (%) and compared using Pearson’s χ² test. Statistical significance was considered at a probability of P value < .05.

RESULTS AND ANALYSIS

Patients

A total of 48 patients with acute burns were identified to have received ulinastatin during the period starting from October 05, 2012; these comprised the ulinastatin group. The control group included 49 subjects admitted to the hospital before October 05, 2012, starting from February 05, 2011. Thus, a total of 97 patients were enrolled in the study. All patients belonged to Asian race. The mean age of patients in the ulinastatin and control groups were 37.8 ± 14.1 and 35.3 ± 17.8 years, respectively. The male:female distribution in the ulinastatin group was 1:1 and 1:1.72 in the control group. The mean body temperature, systolic and diastolic blood pressures, hematocrit, leukocyte count, platelet count, serum creatinine, and serum bilirubin values at baseline in both groups have been provided in Table 1. Patients in the ulinastatin group had a mean burnt BSA of 60.1%, while in the control group, it was 58.6%. The distribution of patients across different strata (<40%, 41–60%, 61–80%, and >80%) of burnt BSA was similar between the groups (Table 2). A similar proportion of patients in the ulinastatin group and control

Table 1. Demographic and baseline characteristics

| Particular                        | Ulinastatin (N = 48) | Control (N = 49) | P Value |
|-----------------------------------|----------------------|------------------|---------|
| Age (y) mean (SD)                 | 37.8 (14.1)          | 35.3 (17.8)      | .1      |
| Gender (male:female)              | 24:24                | 18:31            | .19     |
| Burnt surface area (%) mean (SD)  | 60.1 (18.4)          | 58.6 (25.7)      | .7      |
| Inhalation injury (yes:no)        | 12:36                | 11:38            | .8      |
| Temperature (°C) mean (SD)        | 101.4 (1.6)          | 98.8 (1.0)       | <.0001  |
| Hematocrit (%) mean (SD)          | 36.5 (7.4)           | 42.6 (10.0)      | .001    |
| Leukocyte count (/mm³) mean (SD)  | 11,054 (8065)        | 21,887 (14,040)  | <.0001  |
| Platelet count (/mm³) mean (SD)   | 198,000 (119,981)    | 316,200 (185,251)| .0002   |
| Serum creatinine (mg/dL) mean (SD)| 0.9 (0.54)           | 1.2 (1.39)       | .166    |
| Serum bilirubin (mg/dL) mean (SD) | 1.46 (1.27)          | 1.04 (1.1)       | .085    |
| Systolic BP (mm Hg) mean (SD)     | 130.4 (16.0)         | 128.2 (19.6)     | .55     |
| Diastolic BP (mm Hg) mean (SD)    | 72.4 (10.7)          | 76 (14.0)        | .16     |
group (25% and 22.4%, respectively), were diagnosed to have inhalation injury identified by clinical manifestations and radio-imaging findings (pulmonary edema, congestion, effusion, etc).

Study Drug Use
The patients in the ulinastatin group received ulinastatin in addition to standard care; the commonly used regimen was 100,000 IU given as intravenous infusion every 8 to 12 hours, dissolved in normal saline and given over 30 to 60 minutes. The mean duration of ulinastatin use was 8.8 days (range 1–26 days), and the mean cumulative dose was 2,400,000 IU (Table 3).

Length of Hospital Stay
The median hospital LOS was higher in the ulinastatin group compared with the control group (20.5 days vs 9.5 days). Similarly the median ICU LOS was also higher in the ulinastatin group (15.5 days vs 6 days). The median duration of hospital LOS was higher in the ulinastatin group, both in survivors (61 days vs 36.5 days) and nonsurvivors (13 days vs 6 days; Table 4).

Mortality Rates
The overall in-hospital mortality among the studied patients was 68% (66 of 97). The in-hospital mortality (Table 5) was higher (75.5%) in the control group than in the ulinastatin group (60.4%; Figure 1). All patients (11 in ulinastatin group and 14 in control group) with more than 80% burnt BSA had died. In patients with burnt BSA < 40%, a similar proportion had died in both the groups (40% in ulinastatin and 46.2% in control). In patients with 41 to 80% burnt BSA, 16 of 32 had died in the ulinastatin group, while 17 of 22 had died in the control group (Figure 2). This difference was statistically significant (77.27% vs 50%; P = .04; Table 6). Seventy-five percent (9 of 12) of patients with inhalation injury in the ulinastatin group and 91% (10 of 11) of similar patients in the control group had died.

DISCUSSION
In India, the incidence of burn injuries continues to be high, with more than 1,000,000 people moderately or severely burnt every year, making it an endemic health hazard. The mortality rates reported in studies from tertiary centers in India range from 40 to 68%. This retrospective single-centre case note review analysis showed lower mortality in patients hospitalized for acute burns when ulinastatin was added to the standard care of therapy.

The pathophysiology of the burn wound involves an inflammatory reaction leading to rapid edema formation as a result of increased microvascular permeability accompanied by vasodilation and increased extravascular osmotic activity. Lipid peroxidation, leading to generation of reactive oxygen species, plays a critical role in burn-induced plasma leakage by contributing to the increased microvascular permeability, edema formation, and tissue damage after burn injury. Septicemia/sepsis, shock, and multiorgan failure are recognized as the most common causes of death in burn injury patients. Burn shock can develop rapidly after major burn injury, and current treatment mainly includes early

Table 2. Distribution of cases based on burnt BSA in the two groups

| Burnt BSA (%) | Group | Ulinastatin (n) | Control (n) |
|--------------|-------|----------------|-------------|
| <40          | 5     | 13             |
| 40–80        | 32    | 22             |
| ≥80          | 11    | 14             |

*p* value = .11.

Table 3. Ulinastatin use summary

| Ulinastatin | N  | Mean Duration | Mean Dose | Median Dose |
|-------------|----|---------------|-----------|-------------|
|             | 48 | 8.8 days      | 2,400,000 IU | 2,550,000 IU |

Table 4. Hospital and ICU length of stay among survivors and nonsurvivors

| Population | Hospitalization (Median) Days | ICU Stay (Median) Days |
|------------|--------------------------------|------------------------|
|            | Ulinastatin Group | Control Group | Ulinastatin Group | Control Group |
| All patients | 20.5 | 9.5 | 15.5 | 6 |
| Survivors   | 61    | 36.5 | 24    | 12 |
| Nonsurvivors| 13    | 6    | 13    | 6    |

*ICU*, intensive care unit.

Table 5. Mortality in the two groups

| Group | Ulinastatin (n) | Control (n) | *χ*² Test | *P* Value |
|-------|----------------|-------------|-----------|-----------|
| Died  | 29 (60.4%)     | 37 (75.5%)  |           | 0.19      |
| Survived | 19 (39.6%) | 12 (24.5%)  |           |           |
adequate fluid resuscitation with the aim of maintaining sufficient tissue perfusion. However, shock can develop and progress despite fluid resuscitation. Patients with larger burns often develop prolonged hypermetabolism, chronic inflammation, and lean body mass wasting, all of which may impair wound healing. The associated alteration in the immune status increases the susceptibility to infection via the burn wound, further exacerbating systemic inflammation.

Increased serum levels of proinflammatory cytokines characterize the systemic response to burns. Cytokines, including interleukin (IL) 1β and tumor necrosis factor α, contribute to the production of fever, acute-phase proteins, and an overall state of catabolism. They also upregulate the production of prostaglandin E2, IL-6, and platelet-activating factor by endothelial cells and macrophages. High levels of IL-6 have been associated with increased rates of morbidity and mortality. There is a paucity of therapies specifically aimed at controlling these events. Even in the developed world, despite the practice of advanced surgical techniques and availability of tissue-engineered biomaterials, management of burns and their sequelae remains a challenge.

There has been no major breakthrough in the treatment of burns since many years now, and with the increasing resistance of bacteria to antimicrobials, the management of burns patients has become more complicated. Therapies aimed at controlling the inflammation and improving the immunological integrity have a role in treatment and can improve outcomes in such patients. These therapies can act as adjuvants to antimicrobials and fluid management.

Ulinastatin (also known as urinary trypsin inhibitor, HI-30, or bikunin) is a multifunctional
Kunitz-type serine protease inhibitor belonging to the IαI family, produced by hepatocytes and found in human urine and blood. During inflammation, ulinastatin is cleaved from IαI family proteins through proteolytic cleavage by neutrophil elastase in the peripheral circulation or at sites of inflammation.\textsuperscript{7–9} It has inhibitory action on a wide variety of serine proteases, including trypsin, thrombin, chymotrypsin, kallikrein, plasmin, elastase, cathepsin, and factors IXa, Xa, XIa, and XIIa. It also inhibits inflammation by suppressing the infiltration of neutrophils and release of elastase and inflammatory mediators from neutrophils. Ulinastatin also inhibits the production of tumor necrosis factor α, IL-1, and IL-6 possibly through the suppression of mitogen-activated protein kinase (MAPK) signaling pathway.\textsuperscript{7–9} It also inhibits coagulation and fibrinolysis, which promotes microperfusion.\textsuperscript{7,8} Thus, ulinastatin acts as an agent for control of inflammation and immune modulation to prevent organ dysfunction and promote homeostasis. Based on these mechanisms and clinical evidence, ulinastatin is approved for management of multiple occurrences in patients with conditions like sepsis, acute pancreatitis, and acute circulatory failure due to hemorrhagic, bacterial, or traumatic shock in countries like Japan, China, South Korea, and India.

Luo et al, in 2013,\textsuperscript{12} reported attenuation of increase in vascular permeability and net fluid accumulation along with reduced fluid requirements in a swine model with 40% TBSA burn injury, with the use of ulinastatin. Ulinastatin has also been studied in other animal models of burn injury and has demonstrated significant decrease in the levels of inflammatory mediators, oxygen-free radicals, and protective effect on multiple organs.\textsuperscript{10–14} Many of these findings have been substantiated in clinical studies in limited number of patients with severe burn and severe burn–induced sepsis, which have reported decrease in inflammatory mediators, edema, and wound size, accompanied by reduced morbidity and mortality.\textsuperscript{14–16}

Multiple studies in India have reported overall mortality rates ranging from 40.3 to 68.5% among burn injury patients.\textsuperscript{17–22} The observed overall mortality of 68% in this study is in line with these reports. These values are, however, much higher than those reported from the developed world. The American Burn Association-National Burn Repository 2015 (ABA-NBR 2015) reported an overall mortality of 3.2% among more than 172,000 burn injury patients from different centers across the United States.\textsuperscript{27} Similarly, a systematic review of more than 186,500 patients from 76 studies by Brusselaers et al\textsuperscript{24} reported that mortality rates usually ranged between 1.4 and 18% (maximum, 34%) in hospitalized burn injury patients in Europe. Burnt BSA appears to be the major determinant here. O’Mara et al, in 2000,\textsuperscript{28} reported a mortality of 72% among 39 patients with >60% BSA burns admitted to a burn trauma unit in Pennsylvania, PA. The ABA-NBR 2015 data had only 3.1 % cases with a total burn size of 40% BSA or more. Similarly, in the European data, the mean BSA burns was 11 to 24%. These values are in stark contrast to the high mean BSA burns reported in Indian studies, which range from 47.5 to 67%, with 40 to 50% patients having burn size of 60% BSA or more.\textsuperscript{17,19–21} In our study, the mean BSA burns was 60.1% and 58.6% in the ulinastatin and control groups, respectively, and half of the patients in each group had >60% BSA burns.

Age is another important determinant of burn injury outcome, mortality increasing with age.\textsuperscript{29,30} Studies conducted in India have also shown increasing mortality with increase in mean age of the patients.\textsuperscript{17–20} The mean age (37.8 years in ulinastatin group and 35.3 years in control group) and mortality in this study correlates well with that reported by Subrahmanyam and Joshi, in 2003,\textsuperscript{17} in a retrospective study of 254 patients, with a mean age of 38 years and an overall mortality rate of 68.5%.\textsuperscript{20}

The mortality in the ulinastatin group (60.4%) was, however, lower than in the control group (75.5%). The difference in mortality between the groups was more evident in those belonging to the intermediate stratum of burnt BSA (41–80 %). There was a significantly lower incidence of mortality in the ulinastatin group, than in the control group, in this stratum (50% vs 77.27%; \(P = .04\)).

In many low- and middle-income countries, mortality increases and reaches a plateau of 100% at 60% BSA burned.\textsuperscript{3} Even in developed countries where resources are abundant, treatment failure is a common occurrence in patients with BSA burns of more than 60%.\textsuperscript{28} In this study, all patients with >80% BSA burns died; however, notably, although in the control group all patients with > 60% BSA burns died, 41.7% (5 of 12 patients) of those with 61 to 80% BSA burns survived in the ulinastatin group. This finding, in addition to earlier Indian studies that

### Table 6. Mortality rates based on burnt BSA strata

| Burnt BSA | Ulinastatin Group | Control Group | \(\chi^2\) Test |
|-----------|------------------|---------------|---------------|
| <40 %     | 2/5 (40%)        | 6/13 (46.2%)  | .81           |
| 41–80%    | 16/32 (50%)      | 17/22 (77.27%)| .04           |
| >80%      | 11/11 (100%)     | 14/14 (100%)  | 1             |

Bold indicates statistical significance of \(P\) value.
have reported a 100% mortality in patients with >55 to 60% BSA burns, indicates a favorable impact of ulinastatin in patients with large area burns. As per ABA-NBR 2015 data, nonsurvivors generally tend to have shorter LOS compared with survivors; and among the survivors, the hospital stay was approximately 1 day for each percent BSA burns. A prospective study in 278 patients by Macedo and Santos, in 2007, indicated that shorter hospital LOS, among other factors, predicted increased mortality. The mean LOS reported in the study was 17.2±14.9 days among nonsurvivors and 11.9±9.3 days among survivors. The review by Brusselaers et al reported a mean LOS in the general population with burn injuries of 7 to 33 days (median, 3–18 days). Bain et al, in 2014, in a retrospective analysis of 2499 patients from central India also reported lower median LOS (4 days) of stay in nonsurvivors compared with overall LOS of 8 days. Akther et al, in 2010, in a prospective and prospective study of 714 burns patients admitted in the surgery department of a tertiary hospital in India reported a mean LOS of 11 to 30 days in those who died and >30 days in those who survived. Shorter duration of hospitalization is associated with death and, thus, is not a predictor of mortality but rather a consequence of the outcome. The median LOS was higher in the ulinastatin group (20.5 days) compared with control group (15.5 days). This was also reflected in LOS for both survivors and nonsurvivors, which were higher in the ulinastatin group compared with the control group.

LIMITATIONS

This was a small, retrospective case note study, and comprehensive details of important variables like serial values of laboratory parameters at specific time points, development of infection, surgical intervention, need for blood transfusion, presence of multiresistant bacteria in wound, presence of fungi in wound, etc were not available for analysis and hence not studied. Our study was limited to in-hospital events only and hence longer term outcomes have not been considered. Finally, detailed study of associated morbidity was also not possible. Thus, it can be used only to generate a preliminary hypothesis and additional testing.

CONCLUSION

Burn injury continues to be a challenge to treat and is associated with significant mortality in those with larger area of burns. In the absence of any major medical breakthrough in the treatment of burns in recent years, therapies that control inflammation and improve the immunological integrity can prove useful adjuvants to fluid management and antimicrobials. Ulinastatin, a serine protease inhibitor, by achieving this, might be a useful addition to burns treatment regimens. In this study, ulinastatin when added to current standard therapy of burns appeared to reduce mortality. This benefit was more prominently observed in those with intermediate extent (40–80%) of burnt BSA. It also increased the time to death in those who died, as evident from the increased hospital LOS in them.

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