Prevention of Exposure Keratopathy in the Intensive Care Unit: Evaluation of an EMR-Based Lubrication Order Protocol for Ventilated Patients

Cole J. Swiston, MD[1] K.S Hu, MD[1] A Simpson, MD[1] E Burton, MD[2] B.J Brintz, PhD[3] A Lin, MD[1]

[1] Department of Ophthalmology, John A. Moran Eye Center, University of Utah, Salt Lake City, Utah
[2] Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, Maryland
[3] Division of Epidemiology, Department of Internal Medicine, University of Utah, Salt Lake City, Utah

Address for correspondence Cole J. Swiston, MD, John A. Moran Eye Center, 65 N Mario Capecchi Dr, Salt Lake City, UT 84132-5230 (e-mail: Cole.Swiston@hsc.utah.edu).

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Abstract

Purpose In this pilot study, we aimed to investigate the efficacy of an electronic medical record (EMR) order set for lubricating ointment (four times daily) in the prevention of exposure keratopathy in ventilated patients in the intensive care unit (ICU) at the University of Utah. We attempted to capture the magnitude of morbidity, cost, and care burden in ventilated patients, as well as the utility of a systematic EMR-based preventative lubrication protocol in the ICU setting.

Methods After implementation of the order set, a retrospective chart review was performed to capture all ventilated ICU patients pre- and postintervention. Three separate study periods were used: (1) Six months prior to coronavirus disease 2019 (COVID-19) and prior to the ocular lubrication intervention; (2) the subsequent 6-month period including COVID-19 patients but prior to any intervention; and (3) the subsequent 6-month period postintervention, including COVID-19 patients. The primary endpoint of ointment use per day was analyzed with a Poisson regression model. Secondary endpoints including rates of ophthalmologic consultation and exposure keratopathy were compared with Fisher's exact test. A poststudy survey of ICU nurses was included.

Results A total of 974 ventilated patients were included in the analysis. Ointment use per day increased by 155% (95% confidence interval [CI] 132–183%, $p < 0.001$) following the intervention. Rates also increased 80% (95% CI 63–99%, $p < 0.001$) during the COVID-19 study period but prior to intervention. The percentage of ventilated patients requiring a dilated eye exam for any indication was 3.2, 4, and 3.7% in each of the study periods, respectively. There was an overall down trend in the rate of exposure keratopathy which was diagnosed in 33.3, 20, and 8.3% of those receiving ophthalmologic consultation, though these rates were not statistically significant.

Keywords
- exposure keratopathy
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Conclusion These preliminary data show a statistically significant increase in the rates of lubrication in mechanically ventilated patients using an EMR-based order set in the ICU setting. There was no statistically significant decrease in the rates of exposure keratopathy. Our preventative protocol with lubrication ointment was of minimal cost burden to the ICU. Further longitudinal and multicenter studies are needed to better assess the efficacy of such a protocol.

Introduction

Exposure keratopathy is broadly defined as corneal damage related to dryness caused by incomplete eyelid closure and loss of the tear film. The intensive care unit (ICU) environment is particularly conducive to the development of exposure keratopathy in critically ill, ventilated patients primarily due to lagophthalmos. There are several contributing factors in the development of lagophthalmos in ventilated patients, including reduced muscle tone and blink reflex secondary to the use of sedating and neuromuscular blocking agents. Bell's phenomenon is also impaired with the use of these medications, furthering corneal exposure. Mechanically ventilated patients exhibit increased jugular venous pressure, often resulting in fluid retention, chemosis, and conjunctival edema, which limit lid closure.[1] Exposure keratopathy is often underdiagnosed given that many ventilated patients are unable to report symptoms; thus, its exact prevalence in the ICU setting remains unknown. One meta-analysis reported an incidence of 21 to 42% of all ICU patients.[2] Another prospective study strictly examining ventilated patients found rates as high as 57%.[3]

Unrecognized exposure keratopathy can progress to vision-threatening sequelae such as bacterial keratitis, corneal scarring, perforation, and even enucleation in severe cases. Without prevention, exposure keratopathy requires inpatient ophthalmology consultation, possible procedural intervention, and lengthy follow-up. Management of this disease has the potential for marked morbidity and cost implications. As such, a systematic preventative strategy is of critical importance for patient care and health system burden.

Various approaches have been studied, with the main methods including increased surface lubrication by tear film supplementation and/or prevention of evaporation. Data-driven preventative strategies include artificial tears, lubricating ointment, eyelid taping, polyacrylamide hydrogel occlusive dressing, and moisture chambers.[4–8] Studies have shown that compared with lubricating ointment or occlusive methods, artificial tears are inferior, likely owing to their quick evaporation time and need for frequent instillation.[5] Data are mixed comparing polyacrylamide hydrogel, polyethylene covers, and moisture chambers to lubricating ointment. A 2009 prospective study ($n = 40$) using a polyacrylamide hydrogel, Geliperm (Geistlich and Sons Ltd), versus a lubricating ophthalmic ointment, Lacrilube (Allergan UK), showed no difference in the maximal corneal exposure score between the groups.[6] In contrast, a U.K. study found that 90% ($n = 10$) of ventilated patients developed exposure with Geliperm (Geistlich and Sons Ltd) versus 15% ($n = 2$) with Lacrilube (Allergan UK).[7] In regards to moisture chambers, a 2008 meta-analysis showed exposure rates of 7.1% ($n = 113$) in a moisture chamber group versus 21.2% ($n = 151$) with lubricating ointment. In contrast, a 2014 meta-analysis showed no statistically significant difference in rates of exposure between moisture chambers and lubricating ointments ($p = 0.38$).[8] Given these mixed data, a preventative strategy should be chosen based on noninferiority, ease of administration, and cost. Some institutions have adapted a simple protocol implementing the use of lubricating ophthalmic ointment every 4 to 6 hours, avoiding more costly measures such as moisture chambers or polyacrylamide hydrogel dressings. The University of Iowa has adopted this strategy and included lubricant ointment every 6 hours with standard ICU admission order sets; however, the actual utilization of ointment in ventilated patients and overall rates of exposure keratopathy after this intervention were not measured.[9]

In this pilot study, we aimed to assess evidence for the efficacy of an electronic medical record (EMR) order set which automatically selects lubricating ointment to be administered to both eyes every 6 hours in each ventilated patient in the ICU at the University of Utah.

Methods

This study was approved by the University of Utah Institutional Review Board (IRB #00134721). In collaboration with the Huntsman Cancer Hospital Intensive Care Unit (HICU) and the Medical ICU (MICU), the existing order set in the EMR used at the initiation of intubation for all ventilated patients was amended to include an automatically selected ocular lubrication order. The order included ocular lubricating ointment administered every 6 hours in both eyes while the patient is ventilated and was initiated on October 15, 2020.

All ventilated patients in the HICU and MICU spanning an 18-month period were included in the study. Patients were identified in the electronic health record and divided into the following cohorts based on time period: (1) Six months prior to the first diagnosis of coronavirus disease 2019 (COVID-19) in the state of Utah on March 6, 2020 and prior to the ocular lubrication intervention; (2) the subsequent 6-month period including COVID-19 patients but prior to any intervention; and (3) the subsequent 6-month period postintervention,

including COVID-19 patients. For all patients, basic demographic data was collected, in addition to primary medical diagnosis, number of days on the ventilator, doses of ocular lubricating ointment, the presence of an ophthalmologic consultation, primary ocular diagnosis, diagnosis of exposure keratopathy, and any ophthalmic procedure performed. If an official date and time of extubation was not found, the time of death was considered to be that of extubation. Doses of ointment were tracked using the medication administration record, and nursing staff were required to document each dose administered. The diagnosis of exposure keratopathy was determined based on ophthalmologic consultation for any indication. Therefore, only patients requiring an ophthalmologic exam could be diagnosed. Patients were excluded from statistical analysis if their primary ocular diagnosis confounded accurate identification of ocular surface disease related to exposure keratopathy (i.e., Stevens–Johnson syndrome, herpes zoster ophthalmicus, and ocular graft versus host disease).

The primary outcome was the rate of ocular lubricating ointment use (measured in doses per day while on the ventilator) prior to and after intervention. Secondary outcomes included the number of exposure keratopathy diagnoses and the number of ophthalmologic consultations before and after intervention. For the primary outcome of ointment use, a zero-inflated Poisson regression model was used to account for excess zeros in the response and controlled for age and gender using fixed effects.[10] Additionally, we used the likelihood ratio test to assess evidence of a general trend over the full time period and seasonal sine and cosine curves with varying periodicities. Bootstrapping (1,000 iterations) was used to generate 95% confidence intervals (CIs) for estimates of average doses/day over time. Given the small number of responses, Fisher's exact test was utilized for the secondary outcomes including rates of ophthalmologic consultations and exposure keratopathy.

Following data collection, a short survey was distributed to all nurses working in the targeted ICUs. Survey respondents were asked about their role in the ICU, in which ICU they worked, and whether they were aware that the protocol for caring for ventilated patients includes administration of ophthalmic lubricating ointment to both eyes every 6 hours. Respondents were also asked to estimate the number of doses of ointment that they administered per day for a given intubated patient and the number of days that a tube of ointment typically lasted. Finally, respondents were asked to indicate any obstacles they faced in applying the ointment as prescribed and reasons for termination of ointment administration prior to extubation. Questions were asked on an anonymous, voluntary basis as multiple-choice questions with the option to contribute free-form responses.

Results

A total of 974 ventilated patients spanning the three study periods of interest were identified. The mean age was between 54 and 57 years of age and over half of the patients were male (►**Table 1**). The average mortality for our study population was 43.9%. Patients were ventilated on an average of 5.6 days (standard deviation = 7.8). The percentage of COVID-19 patients in each study period was 0, 13.7, and 20.7%, respectively. On average, the mean doses of ointment/day increased in subsequent periods, with an average of 0.3 doses per day in the preintervention and pre-COVID period, 0.7 preintervention but post-COVID, and an average of 2.6 doses per day after implementation of the lubricating ointment order set (►**Table 1**). Using a 30-day moving average (center-aligned) of lubricating ointment doses per day, there was a steady average daily dose rate with some level of seasonality followed by a strong increase around the point of the policy change (►**Fig. 1**).

After accounting for age, gender, and seasonality with a Poisson model (periodicity of 4/year after model fit), the period in which COVID cases were apparent in Utah (prior to intervention) had an 80% increase in the rate of doses per day (95% CI 63–99%, $p < 0.001$). Following the intervention, that rate increased by 155% (95% CI 132–183%, $p < 0.001$). We additionally found much smaller odds of a receiving zero ointment in the post-COVID periods, reduced by 50.9% post-COVID but preintervention and 94.5% postintervention. There was no evidence of a general trend over the full time interval improving model fit. ►**Fig. 2** visually demonstrates

Table 1 Descriptive statistics of ventilated patients during each study period

Variable	Pre-COVID period: $N = 279$	COVID period: $N = 373$	Intervention period: $N = 322$
Age at admission, mean (SD)	54.5 (16.3)	56.6 (15.0)	54.3 (15.0)
Median (IQR)	57.0 (43.0–67.0)	60.0 (47.0–67.0)	57.0 (42.2–65.0)
Range	(18.0–89.0)	(18.0–89.0)	(19.0–88.0)
Gender, M	144 (51.6%)	203 (54.4%)	186 (57.8%)
Doses of ointment/day, mean (SD)	0.3 (1.2)	0.7 (1.4)	2.6 (2.0)
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.4)	3.2 (0.1–4.1)
Range	(0.0–9.3)	(0.0–6.7)	(0.0–8.0)
Ophthalmology consult	9 (3.2%)	15 (4%)	12 (3.7%)
Diagnoses of exposure, Yes	3 (33.3%)	3 (20%)	1 (8.3%)

Abbreviations: COVID, coronavirus disease; IQR, interquartile range; M, male; SD, standard deviation.

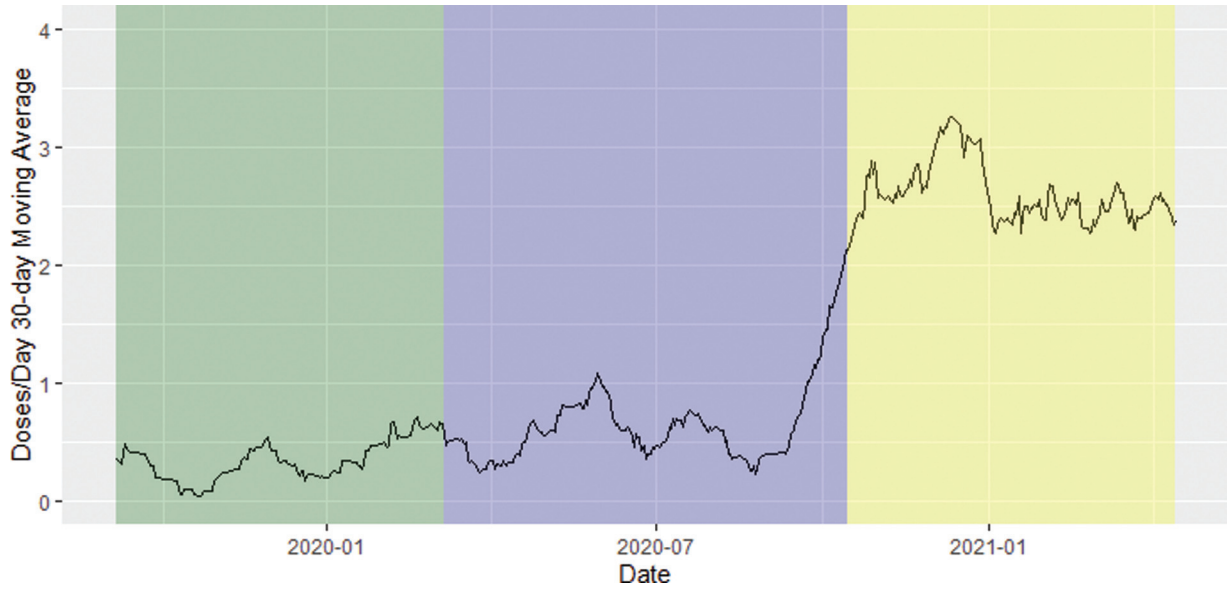

Fig. 1 A 30-day moving average doses of ointment per day. The pre-coronavirus disease (COVID) period is highlighted green, the start of COVID period prior to the policy change is highlighted in blue and the official intervention period is highlighted yellow. Note: this is a center-aligned moving average so increases in rate may appear to happen sooner than they actually occurred.

the estimated rate of ointment use in doses/day in each period, with seasonality reflected in those estimates.

As for the secondary endpoints, there was overall no evidence of a change in the rate of ophthalmologic consultation ($p = 0.88$). The percentage of ventilated patients requiring a dilated eye exam for any indication was 3.2, 4, and 3.7% in each of the study periods, respectively. The most common indications for an ophthalmologic exam was fungemia (31%, $n = 11$), followed by blurry vision (17%, $n = 6$), redness/discharge (11%, $n = 4$), and evaluation for ocular involvement of a separate systemic disease (11%, $n = 4$). Among this smaller cohort of patients, there was an overall down trend in the rate of exposure keratopathy which was diagnosed in 33.3, 20, and 8.3%, respectively, though there was no evidence of an association between period and exposure keratopathy ($p = 0.37$; ►**Table 1**). One patient developed corneal scarring due to exposure keratopathy in the pre-COVID and preintervention period. There were no permanent ocular surface complications related to exposure during the COVID (preintervention) and postintervention periods.

A total of 50 ICU nurses completed the poststudy survey. Most ($n = 45$, 90%) nurses were aware of the ophthalmic lubricating ointment protocol. On average, nurses communicated that they administered 2.2 doses (median 2 doses) of ophthalmic lubricating ointment per day. Nearly half ($n = 22$, 44%) of nurses reported no obstacles administering the ointment. The most common obstacles that nurses cited

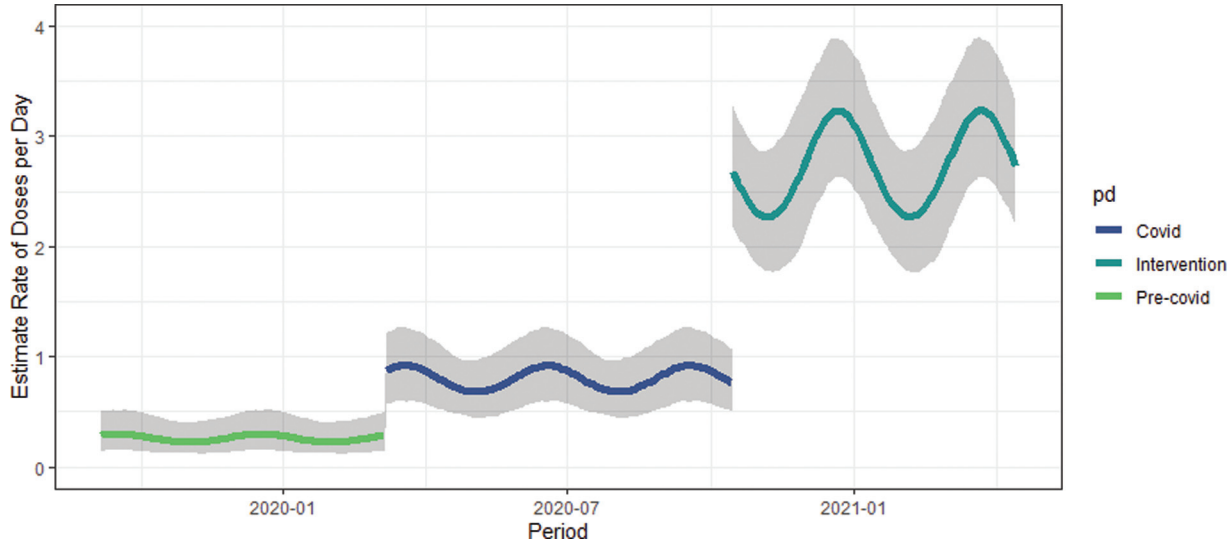

Fig. 2 Estimates and bootstrapped 95% confidence interval (CI) for doses/day by date for male with median age. Note that the estimates for age and gender in the Poisson model are small so this plot is not highly affected by the values chosen for those coefficients.

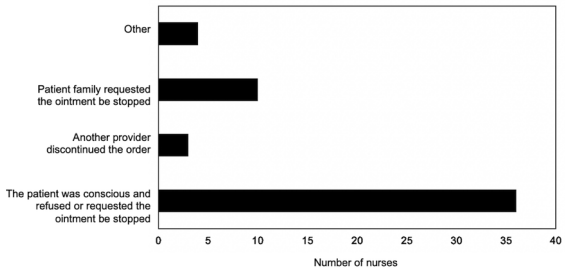

Fig. 3 Obstacles to administration of ophthalmic lubricating ointment.

were the belief that the ointment was not important ($n = 13$, 26%) and being busy with other patient responsibilities ($n = 12$, 24%). Five (10%) nurses also described withholding ointment doses if ointment was still visible in the patient's eyes from previous doses, and six (12%) nurses cited patient prone positioning as an obstacle that made ointment administration challenging (►**Fig. 3**). Nurses commonly stopped administering ointment if the patient was conscious and requested that the ointment be stopped ($n = 37$, 74%). Occasionally, another provider discontinued the order prior to extubation ($n = 10$, 20%). Several nurses commented that they tend to give the ointment as needed when the patient's eyes "appeared dry," and they suggested spacing ointment administration to longer intervals (►**Fig. 4**).

Using the average wholesale price of the ocular lubricating ointment at $2.00 per tube as well as the average number of days each tube lasted, we calculated the cost per average ventilated patient (5.6 ventilator days) at $2.87 per patient. The total cost to each unit was found to be $375 per year in the HICU, and $1,477 per year in the MICU.

Discussion

Sequelae of exposure keratopathy can increase health care burden and significantly decrease patients' vision and quality of life. In this real-world study, we attempted to capture the magnitude of morbidity, cost, and care burden in ventilated patients, as well as the utility of a systematic preventative EMR-based lubrication protocol. To our knowledge, our pilot study is the first of its kind to measure the potential impact and efficacy in the prevention of exposure keratopathy using an EMR-based ophthalmic lubrication order set linked with the intubation of patients in the ICU setting.

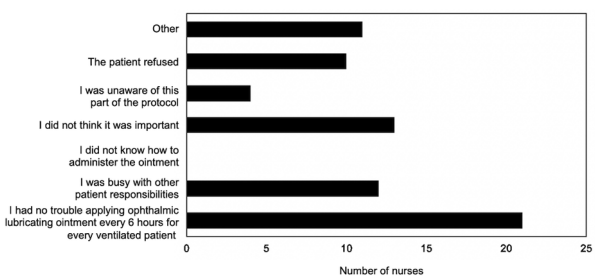

Fig. 4 Reasons for termination of ophthalmic lubricating ointment prior to extubation.

After accounting for age, gender, and seasonality, there was a statistically significant increase in doses of lubrication administered per day following our intervention, though average number of doses per day (2.6) was lower than that specified in the order set. This was in line, however, with the perceived average daily administration gathered via nursing survey at 2.2 doses per day. While 90% of ICU nurses reported that they were aware of the protocol, over half cited barriers such as not thinking lubrication was important and burden of other care responsibilities. Our preliminary data suggest that education with ICU nurses on exposure keratopathy could lead to increased adherence to the protocol orders. It may be postulated, however, that nurses were aware of the decreased rates of ointment administration and that this may reflect those patients who did not display lagophthalmos or had residual ointment remaining in the eyes from prior doses, therefore at low risk of developing exposure keratopathy. We observed a modest and dose-dependent decrease in the rates of exposure keratopathy during each of the study periods. While these rates were not statistically significant, there was only a single case of exposure keratopathy diagnosed after the intervention was implemented, and this was in a patient at particularly high risk for lagophthalmos due to prone positioning in the setting of COVID-19. Particularly at academic institutions, a protocol such as this may decrease routine ICU ophthalmologic consultation burden for residents. Of note, prospective studies investigating the effectiveness of lubricating ointment typically administered ointment more frequently than four doses per day. Lenart and Garrity studied 50 patients who received lubricating ointment every 4 hours while Koroloff et al examined rates in 110 patients given Lacrilube (Allergan Australia Pty Ltd) every 2 hours in addition to lubricating drops. Rates of any corneal epithelial disease in these patient cohorts were 4 and 6.7%, respectively.[4,11] We demonstrated that in an uncontrolled ICU setting and even with an average of 2.7 doses of ointment per day, the rates of clinically significant (requiring ophthalmologic consultation) exposure keratopathy were extremely low at 0.3% ($n = 322$).

As a pilot investigation, this study has several limitations. The data were collected in a retrospective and cross-sectional nature and confined to a single institution. As with any retrospective study among ventilated patients, those who pass away due to systemic illness are not captured. These patients represented 43.9% of our cohort. There was also the added confounder of COVID-19 during the study period. In discussion with our ICU teams, the unexpected increase in average daily ointment during the preintervention COVID period was likely related to an existing long-standing protocol, which includes ointment for any patient placed in prone positioning. We were unaware of this protocol at the onset of the study, and the rising number of ventilated patients with COVID-19 requiring prone positioning likely led to a significant increase in ointment use before implementation of our intervention. The effects of COVID-19 and prone positioning on rates of exposure keratopathy have not been studied to

date. Finally, there were very few patients in either the pre- or postintervention periods who were seen by ophthalmology and diagnosed with exposure keratopathy. A larger sample size or prospective study is needed to determine whether application of lubricating ophthalmic ointment for intubated patients decreases rates of exposure keratopathy. Prospective and longitudinal research are needed to more accurately assess the sustainability and long-term effects of our protocol. Further studies should also be conducted on the efficacy and practicality of alternative and less time-consuming interventions.

Conclusion

An EMR-based ophthalmic lubricating protocol can increase the rates of lubrication in mechanically ventilated patients and has the potential to decrease rates of exposure keratopathy. Our preventative protocol with lubrication ointment was of minimal cost burden to the ICU. Further longitudinal and multicenter studies are needed to better assess the efficacy of such a protocol.

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Conflict of Interest
The authors declare no conflicts of interest.

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