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CME Information: Randomised Controlled Trial of Adult Therapeutic Colouring for the Management of Significant Anxiety in the Emergency Department

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Educational Objectives
After reading the article, participants should be able to discuss the effectiveness of adult coloring books as a treatment for anxiety.

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Randomized Controlled Trial of Adult Therapeutic Coloring for the Management of Significant Anxiety in the Emergency Department

Naveendran Rajendran, Tatum Priyambada Mitra, Sara Shahrestani, MD, and Andrew Coggins, MD

ABSTRACT

Background: Anxiety and acute distress are significant concerns in the emergency department (ED). Adult coloring books are often utilized as an effective means of relaxation in waiting rooms and newsstands, but there are no reported randomized trials examining their effectiveness as a treatment for anxiety.

Methods: We set out to examine the effectiveness of adult coloring books using a randomized placebo-controlled trial at a university-affiliated tertiary ED. Anxiety was measured using a validated self-reporting score, the Hospital Anxiety and Depression Scale (HADS-A), with a range of 0 to 21. Patients with HADS-A ≥ 7 were randomly assigned to either an adult coloring pack (n = 26) or placebo pack (n = 27). The primary outcome measure was the within-patient change in HADS-A scores following 2 hours of exposure.

Results: A convenience sample of 117 patients were screened, and 53 patients were randomized. Characteristics of allocated groups were similar in terms of sex, diagnosis, and ethnicity. A higher proportion of intervention subjects spent ≥1 hour engaged with their activity (46.2% vs. 4.0%, p = 0.01). For the primary outcome measure, the mean within-patient decrease in HADS-A score at 2 hours for intervention subjects was 3.7 (95% confidence interval [CI] = 2.4 to 5.1, p < 0.001) versus a decrease of 0.3 (95% CI = –0.6 to 1.2, p = 0.51) in the placebo group.

Conclusions: Among ED patients, exposure to adult coloring books resulted in lower self-reported levels of anxiety at 2 hours compared to placebo.
Given that the ED is a stress inducing environment, nonpharmacologic therapy for anxiety in the form of art therapy may be useful. Moreover, the Australasian College of Emergency Medicine has recently put forward an aspirational approach to improving care of patients with mental health disorders. Specifically, the recommendation stated that “the ED should be a place that is safe and supportive for all, not a place that people want to escape from. Long, uncertain waits are unacceptable.”10 Further, there is evidence to suggest that unoccupied time in the ED can increase patients’ negative perceptions of their waiting time with a strong association between delays and overall dissatisfaction.11,12

Commonly available adult coloring books have been used extensively in the community as an effective strategy for reducing anxiety,13,14 but have not been formally studied in an ED setting. Art therapy has been hypothesized to be an effective mindfulness strategy that alleviates symptoms of anxiety through cognitive easing.14,15 Prior observational studies have shown that art therapy can reduce symptoms of anxiety in healthy university students and oncology patients in a hospital setting.16–19

Abbing et al.,20 in their 2018 review of the effectiveness of art therapy on anxiety in adults, identified only three studies with a total of 162 patients and concluded that the small sample size and large heterogeneity within the data set made it impossible to perform a meta-analysis. Many systematic reviews evaluating art therapy as a treatment for anxiety suggest potential benefit but conclude that more well-designed randomized controlled trials (RCTs) are required.20–23 These reviews acknowledged the anecdotal evidence that art therapists and other health care professionals experience regarding the impact of art therapy in patient care but called for trials that were randomized and placebo controlled to obtain stronger evidence on the efficacy of art therapy.

Art therapy has a low potential risk of harm and represents a simple short-term intervention in a busy ED setting. Furthermore, art therapy requires little staff supervision, explanation, or facilitation and is low in cost, making it an ideal intervention for the busy ED setting. The purpose of this study was to test the effect of adult coloring books on anxiety in the ED. We hypothesized that patients who spent up to 2 hours engaged with adult coloring book images would experience a significant drop in their anxiety compared with patients who were provided with a placebo.

MATERIALS AND METHODS

Study Design and Setting
This study was conducted at Westmead Hospital, a university-affiliated tertiary center in Sydney, Australia. The Westmead Hospital ED receives around 80,000 presentations a year. Ethical approval was obtained through the Western Sydney Local Area Research Ethics Committee (HREC/17/WMEAD/354) and adhered to Australian national guidelines.24

This study was a RCT comparing adult coloring books to placebo for the treatment of anxiety in the ED. Patients were approached by investigators from Monday to Friday between 8 AM and 6 PM. ED staff were made aware that a “study on anxiety” was occurring and were invited to flag patients for screening. From April 2018 to January 2019, convenience sampling occurred based on the rostered availability of two lead investigators. Patients were asked if they would be willing to participate in a research study related to nonmedical therapy and anxiety in the ED. Following written consent, a validated score, the Hospital Anxiety and Depression Scale (HADS-A) anxiety subscale, was used for screening. The HADS-A was assessed again at 2 hours for patients who were randomized.

Selection of Participants
All patients in the ED treatment area were potentially eligible for the study. Potential patients were flagged as being “anxious” by senior medical officers (residents and consultants), triage nurses, or an ED social worker who then referred them to the research team. For inclusion in the trial it was necessary for participants to be ED patients with “moderate-severe anxiety” (HADS-A ≥ 7). Patients were required to be able to provide informed consent. Patients were excluded if they were age < 16 years, were unable to provide informed consent, were a perceived aggression risk, had a past history of violence, or were Glasgow Coma Score < 15. Figure 2 describes the flow of participants for selection into the trial. The investigators noted that a proportion of the subjects approached for the trial simply declined to participate even prior to being screened for eligibility. Potential reasons for this have been expanded on in the discussion section of this paper.

Interventions
Participants in the intervention arm were provided with a “coloring pack,” which included 10 standardized adult
mindfulness coloring book images and 36 pencils from the “Milan Colored Pencils in Tin” set. The selection of 10 coloring pages from adult art books was based on images described in the prior art therapy literature including mandalas, buildings, and fictitious animals. Control subjects were provided with a “placebo pack” containing a Bic pen and 10 sheets of A4 paper and were instructed to draw or write freely. The placebo pack was chosen as an active control to provide these patients with an activity and thus avoid comparing the intervention with an inactive control.

**Measurements**

There are various validated self-reporting tools for quantifying anxiety including the HADS-A. Further, the HADS-A has been validated in various languages and groups of patients including in the ED. Our review of the literature noted that the HADS-A has an equivalent validity for the screening of anxiety disorders as other more time consuming scales. Previous studies have identified various cut points of ≥7 (scale = 0–21) as being representative of significant anxiety. Therefore, a cut point of ≥7 was selected as the main inclusion criteria.

**Outcomes**

The primary outcome measure was the within-patient change from baseline HADS-A score following 2 hours of therapy (Figure 1). Demographic data collected included age, sex, ethnicity, and prior use of art therapy. Secondary measures included postintervention survey questions quantifying the value of the therapy and engagement with the treatment packs. Engagement was a patient reported estimate of the length of time engaged with the trial packs. Additionally, intervention subjects were asked if they would “recommend the coloring” to other patients (Likert scale = 1–5).

**Power Calculation**

An observational pilot study of 15 patients was conducted by the investigators as an internal quality assurance project at the Westmead Hospital ED. This study estimated the standard deviation (SD) of the within-patient change in HADS-A score over 2 hours was 2.3. For a conservative sample size calculation, we assumed the SD of the within-patient change in HADS-A following 2 hours of exposure to therapy would be 3. Therefore, a sample size of 48 patients (24 per arm) would have an 80% power to detect a difference of 2.5 or more in the mean change of HADS-A for the intervention group compared to the placebo group (two-sample t-test, 5% two-sided significance level). To account for an anticipated 10% dropout rate, a total sample size of 52 patients was finalized.

**Randomization and Blinding**

Sealed study packs (n = 56) were produced containing half placebo and half coloring materials. Allocation of study pack numbers occurred by the generation of random numbers by a statistician. Following consent, patients were screened, and those meeting the inclusion criteria were allocated randomization group by taking a pack blindly from a sturdy box. Blinding was limited given the clear visibility of both the intervention and the placebo but allocation concealment was maintained during the 2 hours of exposure to the activities.

**Data Analysis**

Data were analyzed using IBM SPSS (V24). The mean and SD were used to summarize continuous variables. Frequencies and percentages were used for categorical variables. A two-sample t-test was used to test for differences in the distribution of continuous variables between intervention and control groups. For comparative analysis, mean differences are reported together with 95% confidence intervals (CIs). Chi-square or Fisher’s exact tests were used as appropriate to test for association between categorical variables. Two-tailed tests with a 5% significance level were used throughout.

**RESULTS**

Over 9 months, 117 ED patients aged 16 to 80 years were consented and screened. Sixty-four patients were excluded (Figure 2). Included patients (n = 53) were randomized to either intervention (n = 26) or placebo (n = 27). Baseline characteristics of the groups including sex, age, ethnicity, prior exposure to art therapy, and diagnosis were similar (Table 1). There was a significant difference in length of engagement with the respective activities provided (p = 0.01). Further, 37.0% of participants allocated to placebo engaged with the allocated activity for less than 5 minutes compared to nil in the intervention group.

Table 2 summarizes the distribution of the HADS-A scores at baseline and following 2 hours of therapy. Table 2 also reports on the primary outcome measure.
For the primary outcome, the mean within-patient decrease in HADS-A score after 2 hours of intervention therapy was 3.7 (95% CI = 2.4 to 5.1, \( p < 0.001 \)). The change in HADS-A score at 2 hours in intervention subjects was significantly greater (\( p < 0.001 \)) than the mean placebo group change of 0.3 (95% CI = –0.6 to 1.2, \( p = 0.51 \)). Although, the HADS-A scores did not differ significantly at baseline (\( p = 0.22 \)), the intervention group had higher mean HADS-A scores than the placebo group at baseline. At 2 hours, the intervention group had significantly lower HADS-A scores when compared with controls (mean difference = 3.4, 95% CI = 1.9 to 5.0, \( p = 0.03 \)). A general linear model was used to adjust for the imbalance at baseline. The mean difference between groups at 2 hours adjusted for the baseline HADS-A score was 3.2 (95% CI = 1.6 to 4.7, \( p < 0.001 \)).

The box plot (Figure 3) illustrates the distribution of the primary outcome measure (i.e., the within-patient decrease in HADS-A score from baseline to 2 hours). It appears that the within-patient changes observed in the placebo group were evenly distributed above and below the reference line at zero—corresponding to no significant change in reported anxiety.
By contrast, all except two patients in the intervention group showed an improvement in their HADS-A score after 2 hours of therapy.

The 26 patients allocated to the intervention group were asked if they would recommend coloring (Likert scale of 1 to 5 with 1 being “would not recommend” and 5 being “would recommend”) as a measure of patient satisfaction with the coloring activity. Ten of these patients scored a 5, eleven scored 4, four scored 3, and only one patient scored 1. The average satisfaction score on this scale was 4.2.

**DISCUSSION**

In this RCT we demonstrated a marked reduction in reported anxiety at 2 hours in the coloring therapy.
The mean reported difference between groups at 2 hours adjusted for the baseline HADS-A score was 3.2 (95% CI = 1.6 to 4.7, p < 0.001). Close to half of the patients of the intervention group engaged for over 60 minutes compared to only 15% of the placebo group suggesting that the art therapy was engaging. Further, the majority of patients in the intervention were highly likely to recommend the experience to other patients. Therefore, in selected patients, art therapy represents a simple patient-centered intervention that confers benefit through distraction leading to short-term stress reduction. These findings might be due to the fact that the task of coloring is thought to be an activity that creates a state of mindfulness even in a noisy environment.16,21

**LIMITATIONS**

The main limitations of this study were the relatively small number of patients enrolled and the lack of blinding. Further, given the study was carried out in a single center, caution must be used in extrapolating the results to other settings. Additionally, the intervention and measurement of effect size occurred over a 2-hour period. While this correlates with the length of a typical ED waiting time there is no evidence that the therapeutic effect would be sustained beyond 2 hours. In terms of blinding, the lack of overall blinding was an unavoidable aspect of the study that may have led to bias.36 Care was taken to minimize bias by clearly predefining the inclusion criteria, randomizing patients with the aid of computer-generated tables and maintaining allocation concealment. To minimize response bias, we ensured that participants received standardized instructions and were blinded to the intent of the study.37 To minimize interviewer bias and its potential influence on the self-reported anxiety scores, investigators quantifying the HADS-A scores followed a standardized script and underwent training in using self-reporting questionnaires.36,38 Only three investigators involved in the project administered and recorded HADS-A scores. Using a small number of investigators is likely to have minimized variation in HADS-A score measurement. Another inherent limitation of the study was that patients who had a favorable impression of art therapy could possibly have been more motivated to participate in the trial. As highlighted in Figure 2, a total of 62 of the 179 patients approached for the trial simply declined to participate. Various reasons were cited by patients; common anecdotes included “coloring is not for everyone,” “it’s for children,” or “I am in too much discomfort to engage.” While the results of this study should prevent nonpharmacologic treatments for anxiety being experiences, or intercurrent illnesses could all contribute to severe distress.33 While art therapy represents an opportunity for better ED care at a low cost, we should not assume that a universal provision of this therapy would be either appropriate or effective. Qualitative research on patient experiences with art therapy have revealed that a natural resistance to engagement in art therapy may evoke negative experiences for the patient.34 This may include frustration, fear of failure, and production of negative feelings during or after the art-based experience.35

Figure 3 Box plot of within-patient decrease in Hospital Anxiety and Depression Scale (HADS-A) score at 2 hours.*

![Box plot of within-patient decrease in Hospital Anxiety and Depression Scale (HADS-A) score at 2 hours.](image)}
trivialized by health care staff, showing evidence that alternative treatments can work may not overcome the barriers to engagement that we have observed.

CONCLUSIONS

In summary, this randomized controlled trial examined the provision of therapeutic art therapy versus placebo in a heterogeneous group of patients reporting symptoms of significant anxiety. Given the result strongly favoring a reduction in anxiety with the art therapy intervention, we conclude in line with prior observational studies that the use of therapeutic art in the ED is a reasonable strategy for reducing anxiety. This therapy could be used effectively for both medical and psychiatric patients to mitigate stress during periods of waiting in busy acute hospital settings.

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Video Laryngoscopy Compared to Augmented Direct Laryngoscopy in Adult Emergency Department Tracheal Intubations: A National Emergency Airway Registry (NEAR) Study

Calvin A. Brown III, MD1,2, Amy H. Kaji, MD3, Andrea Fantegrossi, MPH1, Jestin N. Carlson, MD4, Michael D. April, MD, DPhil5, Robert W. Kilgo, MD6, Ron M. Walls, MD1,2, and on behalf of the National Emergency Airway Registry (NEAR) Investigators

ABSTRACT

Objective: The objective was to compare first-attempt intubation success using direct laryngoscopy augmented by laryngeal manipulation, ramped patient positioning, and use of a bougie (A-DL) with unaided video laryngoscopy (VL) in adult emergency department (ED) intubations.

Methods: This study was a secondary analysis of a multicenter prospective observational database of ED intubations from the National Emergency Airway Registry (NEAR). We compared all VL procedures to seven exploratory permutations of A-DL using multivariable regression models. We further stratified by blade shape into hyperangulated VL (HA-VL) and standard-geometry VL (SG-VL). We report differences in first-attempt intubation success and peri-intubation adverse events with cluster-adjusted odds ratios (ORs) with 95% confidence intervals (CIs). We report univariate comparisons in patient characteristics, difficult airway attributes, and intubation methods using descriptive statistics and OR with 95% CI.

Results: We analyzed 11,714 intubations performed from January 1, 2016, through December 31, 2017. Of these encounters, 6,938 underwent orotracheal intubation with either A-DL or unaided VL on first attempt. A-DL was used first in 3,936 (56.7%, 95% CI = 46.9 to 66.5) versus unaided VL in 3,002 (43.3%, 95% CI = 33.5 to 53.1). Of the A-DL first intubations 1,787 (45.4%) employed ramped positioning alone, 1,472 (37.4%) had external laryngeal manipulation (ELM), and 365 (9.3%) used a bougie. Rapid sequence intubation (RSI) was the most common method used in 5,602 (80.8%, 95% CI = 77.0 to 84.5) cases. First-attempt success was significantly higher with all VL (90.9%, 95% CI = 88.7 to 93.1) versus all A-DL (81.1%, 95% CI = 78.7 to 83.5) despite the VL group having more patients with reduced mouth opening, neck immobility, and an initial impression of airway difficult. Multivariable regression analyses controlling for indication, method, operator specialty and year of training, center clustering, and all registry-recorded difficult airway predictors revealed first-attempt success was...
higher with all unaided VL compared with any A-DL (adjusted OR [AOR] = 2.8, 95% CI = 2.4 to 3.3), DL with bougie (AOR = 2.7, 95% CI = 2.1 to 3.5), DL with ELM (AOR = 1.8, 95% CI = 1.5 to 2.2), DL with ramped positioning (AOR = 2.8, 95% CI = 2.3 to 3.3), or DL with ELM plus bougie (AOR = 2.8, 95% CI = 2.3 to 3.3). Subgroup analyses of HA-VL and SG-VL compared with any A-DL yielded similar results (AOR = 2.6 to 3.0; and AOR = 2.4, 95% CI = 1.9 to 3.0, respectively). The propensity score-adjusted odds for first-attempt success with VL was also 2.8 (95% CI = 2.4 to 3.3). Fewer esophageal intubations were observed in the VL cohort (0.4% vs. 1.3%, AOR = 0.2, 95% CI = 0.1 to 0.5).

Conclusions: Video laryngoscopy used without any augmenting maneuver, device, or technique results in higher first-attempt success than does DL that is augmented by use of a bougie, ELM, ramping, or combinations thereof.

Laryngoscopy is a critical skill for the successful resuscitation of ill and injured ED patients. Direct laryngoscopy (DL) has been the historical standard for emergency airway management; however, video laryngoscopy (VL) has been shown to improve glottic view and first-attempt success compared to DL in emergency department (ED) patients and its use in preference to DL has steadily increased.1–4 Maximizing first-attempt success improves patient safety, reduces peri-intubation adverse events, and the available evidence supports the use of VL as the first-line device for emergency airway management.5–7 Glottic view is superior with VL because it effectively places the operator’s eye at the leading edge of the blade, allowing the clinician to see around the base of the tongue and overcoming the challenge of creating a direct line of sight. However, VL systems are more expensive than their DL counterparts and those with hyperangulated blades (i.e., GlideScope, King Vision, and CMAC d-blade) require additional training and practice as the mechanics of intubation differ significantly from standard geometry blades (CMAC, GlideScope teaching blade, McGrath Mac). When an anatomically difficult airway is identified with DL and glottic exposure is poor, commonly taught augmentation maneuvers aimed at improving glottic view include ramped body positioning, external laryngeal manipulation (ELM), and use of a bougie. If success with A-DL is comparable to that of VL, then use of ramping, laryngeal manipulation, and a bougie with a direct laryngoscope may be an alternative to more expensive video devices. Data are lacking regarding how A-DL compares to VL in the ED. Our objective was to compare unaided VL (VL without the use of a bougie, ramped patient positioning, or ELM) to combinations of A-DL for adult ED intubations. Given technique differences based on blade design, we performed subgroup analyses looking at hyperangulated VL (HA-VL) and standard-geometry VL (SG-VL) separately. Our primary and secondary endpoints are first-attempt success and rates of peri-intubation adverse events, respectively.

METHODS

Study Design
We analyzed data from the National Emergency Airway Registry (NEAR), a prospective registry of ED intubations performed at a network of 25 academic and community hospitals. Each participating center obtained internal review board approval prior to data collection.

Data Collection
Intubating providers entered all registry data into a secure Web-based data collection form requiring institutional-specific login credentials and passwords (StudyTRAX, version 3.47.0011; ScienceTRAX). Variables collected included patient demographics, body habitus, estimated weight, preintubation hemodynamics, methods of preoxygenation, initial impression of airway difficulty (i.e., the operator’s initial gestalt of anatomic airway difficulty), difficult airway characteristics (e.g., mouth opening, Mallampati score, neck mobility, presence of airway obstruction, thyromental distance), intubation position and device, medications and doses, operator characteristics, first-pass intubation success or failure, peri-intubation adverse events, and patient disposition. As with other NEAR studies, an intubation attempt was defined as any insertion of a laryngoscope beyond the teeth whether or not an endotracheal tube (ETT) was passed. First-attempt success was defined as a properly placed tracheal tube during the first laryngoscopic attempt, confirmed by either colorimetric or quantitative end-tidal CO2. An adverse event was defined as any undesirable incident that occurred during or immediately after the intubation (i.e., dental trauma, hypoxia, cardiac arrest) or as a result of medication administration (i.e., medication error). After data upload, study investigators reviewed all data,
using quality assurance algorithms to identify and correct data entry errors. We set a minimum registry-wide reporting average of 90% of total identified intubations. The study coordinator (AF, Brigham and Women’s Hospital, Boston, MA) performed active compliance monitoring to ensure the 90% threshold was maintained by cross-referencing captured intubations with each site’s online entries. We reported all data in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (www.strobe-statement.org).8

Study Population
Patients older than 14 years of age intubated at participating NEAR sites from January 1, 2016, through December 31, 2017, were included in this analysis. Periods of participation varied for individual centers because facilities joined NEAR on a rolling basis. We included patients for whom either unaided VL or A-DL was the device chosen for the first intubation attempt. Unaided (or “worst case”) VL was specifically chosen in an effort to see how augmenting DL with non-invasive and inexpensive adjuncts performs against more expensive video enhancement. We excluded encounters with missing device, method or outcome variables.

Outcome Measures
The primary outcome was the difference in first-attempt success between unaided VL and various permutations of A-DL. We categorized A-DL as DL plus ramped position, DL plus bougie, DL plus ELM, DL plus Bougie or DL plus ELM, DL plus both bougie and ELM, DL plus all three maneuvers, and finally, all A-DL attempts. The secondary outcomes included percentages of patients experiencing single and composite peri-intubation adverse events.

Data Analysis
We exported data from StudyTRAX to SAS v 9.4 for statistical analysis. We first described the binomial distributions of first-pass success for VL and DL, the latter stratified by the seven exploratory models defined above and further by blade shape (HA-VL and SG-VL). We then described the differences between the DL and VL cohorts with regards to body habitus, impression of airway difficulty, intubator experience, and predictors of airway difficulty (Mallampati classification, reduced neck mobility or mouth opening, and reduced thyromental distance). We used the Rao-Scott chi-square test, adjusted for within-site correlations and clustering, to compare baseline characteristics which were coded in multiple levels and odds ratios (ORs) with 95% confidence intervals (CIs) to compare baseline characteristics coded in two levels (e.g., initial gestalt of airway difficulty “yes” or “no”). In addition to the variables listed above, we included indication (trauma vs. medical) and method (rapid sequence intubation [RSI] vs. no RSI) for exploratory multivariable models to determine whether A-DL was an independent predictor of first pass success when compared to VL (see Data Supplement S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13851/full, for further details regarding variable coding for the statistical models).

We compared VL to seven exploratory multivariable A-DL models: DL plus bougie, DL plus ELM, DL plus ramped position, DL plus ELM and bougie, DL plus ELM or DL plus bougie, DL plus all three maneuvers, and all A-DL. Since these multivariable models are theory-driven, we included all of the known baseline predictors of first pass success and adverse events, regardless of statistical significance of the univariate comparisons. We report cluster-adjusted ORs and their 95% CI for the covariates. We assess multicollinearity using variance inflation factors (VIF) for each of the covariates. We consider a VIF > 5 to indicate potential multicollinearity. We assess model fit using the Hosmer-Lemeshow goodness-of-fit statistic. We do not assess effect modification with interaction terms, as there were limitations in the numbers with the outcomes of interest and we intended these multivariable models to be exploratory and hypothesis-generating.

Due to the potential for confounding by indication, we also performed a propensity score (for the use of DL) adjusted sensitivity analysis for the primary outcome of first-pass success. The propensity score accounts for use of RSI, body habitus, trauma, Mallampati classification, mouth opening, thyromental distance, neck immobility, whether the intubating provider initially anticipated a difficult airway, and intubator training level.

RESULTS
The National Emergency Airway Registry captured compliant data on 11,714 intubations performed from January 1, 2016, through December 31, 2017. Of
those, there were 6,938 encounters for which the intubating provider first attempted orotracheal intubation with either A-DL or unaided VL. Intubators used A-DL first in 3,936 (56.7%, 95% CI 46.9 to 66.5) versus unaided VL in 3,002 (43.3%, 95% CI = 33.5 to 53.1) of encounters (Table 1). Of the A-DL first intubations, 1,787 (45.4%) employed ramped positioning alone, 1,472 (37.4%) used ELM, and 365 (9.3%) used a bougie (Table 1). A total of 2,128 (30.7%, 95% CI = 24.6 to 36.8) cases had a trauma indication for intubation. Intubators used RSI in 5,602 (80.8%, 95% CI = 77.0 to 84.5) cases and performed intubation without the use of medications 1,108 (16.0%, 95% CI = 12.5 to 19.5) times.

Although the majority of difficult airway characteristics were not assessed, the rates of assessment were similar between groups. The VL group had significantly higher proportions of patients with obese body habitus, neck immobility, reduced mouth opening, and initial operator gestalt of airway difficulty. Operator experience was similar between the two groups (Table 2).

First-attempt success with cluster-adjusted 95% CIs was significantly higher with unaided VL (90.9%, 95% CI = 88.7 to 93.1) versus all A-DL (81.1%, 95% CI = 78.7 to 83.5) despite the VL group having more patients with obese body habitus, reduced mouth opening, neck immobility, and an initial impression of airway difficulty. DL augmented by ramped position, ELM, or bougie yielded first-attempt success percentages of 81.7% (95% CI = 78.9 to 84.5), 70.9% (95% CI = 67.5 to 74.4), and 72.3% (95% CI = 65.8 to 78.9), respectively (Data Supplement S2).

After trauma indications for intubation, use of RSI, operator experience, body habitus, provider assessment of airway difficulty, center clustering, and all registry-recorded predictors of a difficult airway were adjusted for, first-attempt success was higher with unaided VL compared with any A-DL (AOR = 2.8, 95% CI = 2.4 to 3.3). It was also higher compared to DL with bougie (AOR = 2.7, 95% CI = 2.1 to 3.5), DL with ELM (AOR = 1.8, 95% CI = 1.5 to 2.2), DL with ramped positioning (AOR = 2.8, 95% CI = 2.3 to 3.3), or DL with ELM and bougie (AOR = 2.8, 95% CI = 2.3 to 3.3; Table 3 and Figure 1). All models had good Hosmer-Lemeshow fit statistics except model 7 (DL plus all three augmentation maneuvers) due to low numbers. In a subgroup analysis examining only HA-VL and SG-VL, we found similar results with a higher first-attempt success compared with all A-DL with an AOR of 3.2 (95% CI = 2.6 to 3.9) and AOR of 2.4 (95% CI = 1.9 to 3.0), respectively (Tables 4 and 5). We did not find multicollinearity in any exploratory model. The propensity score adjusted odds for first-attempt success with VL was also 2.8 (95% CI = 2.4 to 3.3).

Total reported adverse events were similar between the two groups: 11.1% for VL versus 12.0% for DL (AOR = 0.9, 95% CI = 0.8 to 1.0). However, there were significantly fewer esophageal intubations in the VL cohort (0.4% vs. 1.3%, AOR = 0.2, 95% CI = 0.1 to 0.5).

**DISCUSSION**

Video laryngoscopy use during emergency airway management is increasing over time, while DL use is decreasing, particularly when a difficult airway is anticipated. Multiple ED observational studies support this evolution in clinical practice having shown that VL improves glottic exposure and first-attempt success and reduces the incidence of peri-intubation adverse events. A single-center registry from an academic ED reported that CMAC-facilitated intubations resulted in significantly higher first-attempt success.

---

**Table 1**  
Success VL Versus A-DL

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>First Attempts</th>
<th>First-pass Success</th>
<th>First-pass Success (%)</th>
<th>Cluster-adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaided VL</td>
<td>3,002 (43.3%, 33.5%–53.1%)</td>
<td>2,726/2,998 (4 missing)</td>
<td>90.9%, 88.7%–93.1%</td>
<td></td>
</tr>
<tr>
<td>All A-DL</td>
<td>3,936 (56.7%, 46.9%–66.5%)</td>
<td>3,191/3,934 (2 missing)</td>
<td>81.1%, 78.7%–83.5%</td>
<td></td>
</tr>
<tr>
<td>DL + ramped</td>
<td>1,787 (25.7%, 24.7%–26.8%)</td>
<td>1,459/1,786 (1 missing)</td>
<td>81.7%, 78.9%–84.5%</td>
<td></td>
</tr>
<tr>
<td>DL + bougie</td>
<td>365 (5.3%, 4.7%–5.8%)</td>
<td>264/365</td>
<td>72.3%, 65.8%–78.9%</td>
<td></td>
</tr>
<tr>
<td>DL + ELM</td>
<td>1,472 (21.2%, 20.3%–22.2%)</td>
<td>1,044/1,472</td>
<td>70.9%, 67.5%–74.4%</td>
<td></td>
</tr>
<tr>
<td>DL + ELM or bougie</td>
<td>1,654 (23.8%, 22.8%–24.9%)</td>
<td>1,182/1,654</td>
<td>71.5%, 67.9%–75.1%</td>
<td></td>
</tr>
<tr>
<td>DL + ELM + bougie</td>
<td>183 (2.6%, 2.3%–3.0%)</td>
<td>126/183</td>
<td>68.9%, 61.0%–76.7%</td>
<td></td>
</tr>
<tr>
<td>DL + all three</td>
<td>92 (1.3%, 1.1%–1.6%)</td>
<td>64/92</td>
<td>69.6%, 57.8%–81.3%</td>
<td></td>
</tr>
</tbody>
</table>

A-DL = augmented direct laryngoscopy; DL = direct laryngoscopy; ELM = external laryngeal manipulation; VL = video laryngoscopy.
compared with DL but did not specifically compared VL to A-DL. To our knowledge, no previous studies have performed a deliberate comparison of VL alone to A-DL and, therefore, the performance gap between these two techniques has not been fully quantified. Additionally, recent intensive care unit (ICU)-based studies have yielded conflicting data as to whether VL is superior to DL. One recent ICU-based multicenter randomized trial reported no difference in first-attempt success comparing DL to a McGrath Mac VL, despite significantly better glottic visualization with VL. The majority of patients underwent intubation by internal medicine interns or junior trainees with poorly defined oversight. Given this, the generalizability of these findings remains unclear. A recent meta-analysis of 12 randomized controlled trials of both ED and ICU intubations also reported no difference in first-attempt success between VL and DL. In the four intensive care unit (ICU)-based studies that were included; however, RSI was not performed. An additional three studies were prehospital investigations with one comparing a non-video device (Airtraq) to DL. Most importantly, three-quarters of the studies systematically removed predicted difficult airways, the patient

### Table 2
**Difficult Airway Characteristics for VL Versus A-DL**

<table>
<thead>
<tr>
<th>Variable</th>
<th>DL (n = 3,936), Cluster-Adjusted 95% CI</th>
<th>Unaided VL (n = 3,002), Cluster-Adjusted 95% CI</th>
<th>Rao-Scott Chi-square for General Difference or Effect Estimate, OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body habitus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very thin</td>
<td>209/3,914 (5.3%, 4.6%–6.0%)</td>
<td>100/2,992 (3.3%, 2.7%–4.0%)</td>
<td>Rao-Scott χ² p = 0.02</td>
</tr>
<tr>
<td>Thinnest</td>
<td>637/3,914 (16.3%, 15.1%–17.4%)</td>
<td>470/2,992 (15.7%, 14.4%–17.0%)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1,925/3,914 (49.2%, 47.6%–50.7%)</td>
<td>1,518/2,992 (50.7%, 48.9%–52.5%)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>1,001/3,914 (25.6%, 24.2%–26.9%)</td>
<td>776/2,992 (25.9%, 24.4%–27.5%)</td>
<td></td>
</tr>
<tr>
<td>Morbidly obese</td>
<td>142/3,914 (3.6%, 3.0%–4.2%)</td>
<td>128/2,992 (4.3%, 3.6%–5.0%)</td>
<td></td>
</tr>
<tr>
<td>Initial airway difficulty</td>
<td>1,157/3,935 (29.4%, 28.0%–30.8%)</td>
<td>1,081/3,000 (36.0%, 34.3%–37.8%)</td>
<td>OR = 1.4, 1.1–1.7</td>
</tr>
<tr>
<td><strong>Neck immobility</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>814/3,935 (20.7%, 19.4%–22.0%)</td>
<td>1,491/2,999 (49.7%, 47.9%–51.5%)</td>
<td>OR = 3.8, 2.8–5.1</td>
</tr>
<tr>
<td>Reduced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not assessed</td>
<td>2,658/3,931 (67.6%, 66.2%–69.1%)</td>
<td>Not assessed = 2,093/2,998 (69.8%, 68.2%–71.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mallampati class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>356/3,931 (9.1%, 8.2%–10.0%)</td>
<td>229/2,998 (7.6%, 6.7%–8.6%)</td>
<td>Rao-Scott χ² p = 0.2</td>
</tr>
<tr>
<td>2</td>
<td>461/3,931 (11.7%, 10.7%–12.7%)</td>
<td>329/2,998 (11.0%, 9.9%–12.1%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>331/3,931 (8.4%, 7.6%–9.3%)</td>
<td>223/2,998 (7.4%, 6.5%–8.4%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>125/3,931 (3.2%, 2.6%–3.7%)</td>
<td>124/2,998 (4.1%, 3.4%–4.8%)</td>
<td></td>
</tr>
<tr>
<td>Not assessed</td>
<td>2,658/3,931 (67.6%, 66.2%–69.1%)</td>
<td>Not assessed = 2,093/2,998 (69.8%, 68.2%–71.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mouth opening</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1,618/3,931 (41.2%, 39.6%–42.7%)</td>
<td>965/2,998 (32.2%, 30.5%–33.9%)</td>
<td>Rao-Scott χ² p &lt; 0.0001</td>
</tr>
<tr>
<td>Reduced</td>
<td>479/3,931 (12.2%, 11.2%–12.3%)</td>
<td>487/2,998 (16.2%, 14.9%–17.6%)</td>
<td></td>
</tr>
<tr>
<td>Not assessed</td>
<td>1,834/3,931 (46.7%, 45.1%–48.2%)</td>
<td>Not assessed = 1,546/2,998 (51.6%, 49.8%–53.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Thyromental distance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(No. of finger widths)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>38/3,490 (1.0%, 0.7%–1.3%)</td>
<td>39/2,995 (1.3%, 0.9%–1.7%)</td>
<td>Rao-Scott χ² p = 0.5</td>
</tr>
<tr>
<td>2</td>
<td>533/3,930 (13.6%, 12.5%–14.6%)</td>
<td>408/2,995 (13.6%, 12.4%–14.9%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>816/3,930 (20.8%, 19.5%–22.0%)</td>
<td>530/2,995 (17.7%, 16.3%–19.1%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>673/3,930 (1.7%, 1.3%–2.1%)</td>
<td>50/2,995 (1.7%, 1.2%–2.1%)</td>
<td></td>
</tr>
<tr>
<td>Not assessed</td>
<td>2,476/3,930 (63%, 61.5%–64.5%)</td>
<td>Not assessed = 1,968/2,995 (65.7%, 64.0%–67.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Intubator level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGY-1</td>
<td>360/3,878 (9.3%, 8.4%–10.2%)</td>
<td>382/2,930 (13.0%, 11.8%–14.3%)</td>
<td>Rao-Scott χ² p = 0.2</td>
</tr>
<tr>
<td>PGY-2</td>
<td>1,393/3,878 (35.9%, 34.4%–37.4%)</td>
<td>1,035/2,930 (35.3%, 33.6%–37.1%)</td>
<td></td>
</tr>
<tr>
<td>PGY-3</td>
<td>1,437/3,878 (37.1%, 35.5%–38.6%)</td>
<td>1,095/2,930 (37.4%&lt; 35.6%–39.1%)</td>
<td></td>
</tr>
<tr>
<td>PGY-4</td>
<td>401/3,878 (10.3%, 9.4%–11.3%)</td>
<td>244/2,930 (8.3%, 7.3%–9.3%)</td>
<td></td>
</tr>
<tr>
<td>Fellow</td>
<td>773/3,878 (2.0%, 1.5%–2.4%)</td>
<td>68/2,930 (2.3%, 1.8%–2.9%)</td>
<td></td>
</tr>
<tr>
<td>Attending</td>
<td>210/3,878 (5.4%, 4.7%–6.1%)</td>
<td>106/2,930 (3.6%, 2.9%–4.3%)</td>
<td></td>
</tr>
</tbody>
</table>

A-DL = augmented direct laryngoscopy; DL = direct laryngoscopy; VL = video laryngoscopy.
population in whom one would expect to observe a performance benefit from VL.14 Our findings suggest that VL alone provides higher first-attempt success than DL aided by other maneuvers.

Commonly employed visualization aids, such as ramping (especially in obese patients), laryngeal manipulation, and bougie use, have been studied and advocated for as minimally invasive, low-risk, and inexpensive maneuvers that potentially improves DL performance. It would be helpful to know whether DL, enhanced by these adjuncts, can approach the performance characteristics of VL given the expense, upkeep, and training requirements of video laryngoscope systems as A-DL may be a viable option if VL is not readily available. External laryngeal manipulation allows the operator to manipulate the larynx to optimize, in real time, direct visualization of the glottic opening. An early study of a small convenience sample of ED patients with an initial percent of glottic opening (POGO) of <50% found that the application of ELM improved the glottic view in all study patients and increased their POGO scores by an average of 50% to 60%.15 In a cadaveric trial of laryngeal view augmented by ELM, backward-upward-rightward pressure (BURP), or simple cricoid pressure only, ELM provided greater glottic exposure while undirected cricoid pressure often worsened visualization.16 Our results show that HA-VL and SG-VL facilitates first-attempt success better than DL augmented by ELM or ELM plus bougie use. Ramped positioning can be a helpful maneuver in obese and morbidly obese patients; however, the impact of ramping for other patients is less clear and unproven. We included it in this study since optimal patient positioning during DL is an actively debated topic. In a broad patient cohort undergoing general anesthesia in the operating room, elevating the head was associated with improved glottic view, reduced intubation difficulty, less need for ancillary maneuvers, and shorter intubation times compared with a supine body position or simple head extension.17 In an observational study of 231 ED intubations performed by

<table>
<thead>
<tr>
<th>Model</th>
<th>Unaided VL vs.</th>
<th>Unadjusted OR, 95% CI</th>
<th>Multivariable AOR, 95% CIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>All DL</td>
<td>2.3, 1.9-3.0</td>
<td>2.8, 2.4-3.3</td>
</tr>
<tr>
<td>Model 2</td>
<td>DL + use of bougie</td>
<td>2.2, 1.7-2.8</td>
<td>2.7, 2.1-3.5</td>
</tr>
<tr>
<td>Model 3</td>
<td>DL + ELM</td>
<td>1.5, 1.1-1.9</td>
<td>1.8, 1.5-2.2</td>
</tr>
<tr>
<td>Model 4</td>
<td>DL + ramped</td>
<td>2.4, 1.9-3.1</td>
<td>2.8, 2.3-3.3</td>
</tr>
<tr>
<td>Model 5</td>
<td>DL + ELM + bougie</td>
<td>2.2, 1.8-3.0</td>
<td>2.8, 2.3-3.3</td>
</tr>
<tr>
<td>Model 6</td>
<td>DL + bougie or DL + ELM</td>
<td>1.4, 1.0-1.8</td>
<td>1.7, 1.4-2.1</td>
</tr>
<tr>
<td>Model 7</td>
<td>DL + ELM + bougie + ramped</td>
<td>2.3, 1.8-2.9</td>
<td>2.8, 2.4-3.3</td>
</tr>
</tbody>
</table>

A-DL = augmented direct laryngoscopy; AOR = adjusted OR; DL = direct laryngoscopy; ELM = external laryngeal manipulation; HL = Hosmer-Lemeshow; RSI = rapid sequence intubation; VIF = variance inflation factors; VL = video laryngoscopy.

aAdjusted for trauma versus medical indications, use of RSI, operator experience, body habitus, gestalt of airway difficulty, anatomic predictors of airway difficulty, and clustering between centers. VIF for collinearity was <5 for all models.

Figure 1 Odds of first-attempt success with VL vs. A-DL. A-DL = augmented direct laryngoscopy; VL = video laryngoscopy.
residents, the ramped patient position was associated with improved first-pass success compared to supine positioning.\(^{18}\) In a retrospective study of 528 emergent in-hospital intubations, the ramped patient position, compared to supine, was associated with reduced odds of a composite of complications including difficult intubations, esophageal intubations, hypoxemia, or aspiration.\(^{19}\) Results from randomized trials in both the ICU and the operating room have shown mixed results. One randomized controlled trial of ramped versus sniffing head position during urgent intubations in the ICU found that ramping worsened the Cormack-Lehane grade view of the airway, while a similar study in an operating room population showed significantly better laryngeal views when patients were ramped.\(^{20,21}\) Despite these mixed data, more than one-quarter of all patients in our study were placed in a ramped position. This parallels the percentage of patients listed as being either obese or morbidly obese. Although our study did not compare DL with and without these maneuvers, our results suggest that neither ramping nor ELM is as effective as video image acquisition at facilitating first-attempt success.

A gum elastic bougie acts as an intubation guide that provides the operator with tactile feedback and facilitates successful tube placement when the glottic inlet is not well visualized. Bougies also are used as initial guides by some operators regardless of initial

<table>
<thead>
<tr>
<th>Model</th>
<th>HL p</th>
<th>Unaided HA-VL vs.</th>
<th>Unadjusted OR, 95% CI</th>
<th>Multivariable AOR, 95% CI(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8</td>
<td>All direct</td>
<td>2.5, 1.9-3.4</td>
<td>3.2, 2.6-3.9</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>DL + use of bougie</td>
<td>2.4, 1.8-3.2</td>
<td>3.1, 2.5-3.8</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>DL + ELM</td>
<td>1.6, 1.2-2.2</td>
<td>2.1, 1.6-2.6</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>DL + ramped</td>
<td>2.6, 2.0-3.5</td>
<td>3.2, 2.6-4.0</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>DL + ELM + bougie</td>
<td>2.4, 1.8-3.3</td>
<td>3.1, 2.5-3.9</td>
</tr>
<tr>
<td>6</td>
<td>0.6</td>
<td>DL + bougie or DL + ELM</td>
<td>1.5, 1.0-2.1</td>
<td>1.9, 1.5-2.4</td>
</tr>
<tr>
<td>7</td>
<td>0.6</td>
<td>DL + ELM + bougie + ramped</td>
<td>2.5, 1.9-3.4</td>
<td>3.2, 2.6-3.9</td>
</tr>
</tbody>
</table>

\(^{a}\)Adjusted for trauma versus medical indications, use of RSI, operator experience, body habitus, gestalt of airway difficulty, anatomic predictors of airway difficulty, and clustering between centers. VIF for collinearity was <5 for all models.

---

<table>
<thead>
<tr>
<th>Model</th>
<th>HL p</th>
<th>Unaided SG-VL vs.</th>
<th>Unadjusted OR, 95% CI</th>
<th>Multivariable AOR, 95% CI(^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>All direct</td>
<td>2.1, 1.5-3.0</td>
<td>2.4, 1.9-3.0</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>DL + use of bougie</td>
<td>2.0, 1.4-2.8</td>
<td>2.3, 1.9-2.9</td>
</tr>
<tr>
<td>3</td>
<td>0.4</td>
<td>DL + ELM</td>
<td>1.3, 0.9-1.9</td>
<td>1.6, 1.2-2.0</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>DL + ramped</td>
<td>2.2, 1.5-3.1</td>
<td>2.4, 1.9-3.0</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>DL + ELM + bougie</td>
<td>2.0, 1.4-2.9</td>
<td>2.4, 1.9-2.9</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>DL + bougie or DL + ELM</td>
<td>1.2, 0.9-1.7</td>
<td>1.5, 1.1-1.9</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>DL + ELM + bougie + ramped</td>
<td>2.1, 1.5-2.9</td>
<td>2.4, 1.9-3.0</td>
</tr>
</tbody>
</table>

\(^{a}\)Adjusted for trauma versus medical indications, use of RSI, operator experience, body habitus, gestalt of airway difficulty, anatomic predictors of airway difficulty, and clustering between centers. VIF for collinearity was <5 for all models.
glottic exposure. A recent randomized clinical trial of bougie-first versus stylet-in-tube intubations in ED patients using a standard-shaped CMAC video laryngoscope revealed improved first-attempt success when intubators first placed a bougie compared to an ETT loaded with a malleable stylet. These findings suggest that, at least for standard geometry blades, there may be benefit to augmenting VL by bougie use as well.22

LIMITATIONS

Confounding is a risk in any self-reported observational study and confounding by indication can introduce systemic bias. It is likely that A-DL was performed because of predicted intubation difficulty. We mitigate this by controlling for variables that might impact our primary outcome, including predictors of airway difficulty, and performing a propensity-adjusted sensitivity analysis that additionally controlled for operator experience, method, indication, patient demographics, and starting oxygen saturation. Even so, it is impossible to control for all possible unmeasured clinical variables that may have influenced device choice or intubation success. Additionally, the finding that the VL group had higher proportions of anatomically difficult airways is reassuring and argues against selection bias affecting A-DL performance. Recall bias may have influenced data entry, but we believe that such bias would be evenly distributed across sites and encounters. We strived to minimize such errors by requiring entry of 90% or more of all intubations and encouraging completion of data forms in real time. Finally, we chose to study ramped positioning, ELM, and use of a bougie as our DL enhancements since they are commonly taught, have evidence to support their use (although less so for ramping), and are easily captured in a self-reported registry. However, we cannot confirm that a truly optimal or “best-technique” DL attempt was ever performed since this might include many unmeasured variables such as bed height, location of final blade placement, levels of supervision, and endotracheal tube shape, all of which may offer small but meaningful advantages for any one patient.

CONCLUSIONS

Video laryngoscopy used without any augmenting maneuver, device, or technique results in higher first-attempt success than does direct laryngoscopy that is augmented by use of a bougie, external laryngeal manipulation, ramping, or combinations thereof. We observed fewer esophageal intubations in the video laryngoscopy cohort.

References

12. Sakles JC, Mosier J, Chiu S, Cosentino M, Kalin L. A comparison of the CMAC video laryngoscope to the


Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13851/full

Data Supplement S1. Coding for Difficult Airway Characteristics.

Data Supplement S2. Proportions of Patients Experiencing Adverse Effects.
Association Between Perceived Threat and the Development of Posttraumatic Stress Disorder Symptoms in Patients With Life-threatening Medical Emergencies

Jeena Moss¹, Michael B. Roberts, PsyD², Lisa Shea¹, Christopher W. Jones, MD¹, Hope Kilgannon, MD¹, Donald E. Edmondson, PhD³, Stephen Trzeciak, MD, MPH⁴,⁵, and Brian W. Roberts, MD, MSc¹,⁵

A related article appears on page 173.

ABSTRACT

Background: Our objectives were to test whether during a potentially life-threatening medical emergency, perceived threat (a patient’s sense of life endangerment) in the emergency department (ED) is common and associated with the subsequent development of posttraumatic stress disorder (PTSD) symptoms.

Methods: This study was an ED-based prospective cohort study in an academic hospital. We included adult patients requiring acute intervention in the ED for resuscitation of a potentially life-threatening medical emergency, defined as respiratory or cardiovascular instability. We measured patient-perceived threat in the ED using a validated patient self-assessment measure (score range = 0 to 21, with higher scores indicating greater perceived threat). We performed blinded assessment of PTSD symptoms 30 days after discharge using the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (PCL-5).

Results: Ninety-nine of 113 (88%) patients completed follow-up, with 98% reporting some degree of perceived threat, median (interquartile range [IQR]) perceived threat score 12 (6 to 17), and 72% reported PTSD symptoms in relation to their ED visit (median [IQR] PCL-5 score = 7 [0 to 30]). Patients with respiratory instability had higher median (IQR) perceived threat scores (16 [9 to 18] vs. 9 [6 to 14]) and PCL-5 scores (10 [2 to 40] vs. 3 [0 to 17]) compared to patients without respiratory instability. In a multivariable linear regression model adjusting for potential confounders, greater perceived threat in the ED was independently associated with higher PCL-5 scores (β = 0.79, 95% confidence interval [CI] = 0.15 to 1.42). Among the individual perceived threat items, the feeling of helplessness during resuscitation had the strongest association with PCL-5 score (β = 5.24, 95% CI = 2.29 to 8.18).

Conclusions: Perceived threat during potentially life-threatening emergencies is common and independently associated with development of PTSD symptoms. Additional research to test whether reduction of perceived threat in the ED attenuates the development of PTSD symptoms following potentially life-threatening emergencies is warranted.

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Author contributions: BWR supervised all aspects of the study and takes responsibility for the paper as a whole; BWR, ST, DEE, and MBR conceived this study; BWR, MBR, JM, CJ, LS, and HK acquired the data; BWR, JM, and LS managed the data; BWR, MBR, and ST analyzed the data and interpreted results; and BWR, JM, and ST drafted the manuscript and all authors contributed substantially to its revision. All authors approved the manuscript in its final form.

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The development of posttraumatic stress disorder (PTSD) symptoms secondary to a potentially life-threatening medical emergency has been well described,\(^1\) and patients who suffer from critical illness–related PTSD symptoms are at higher risk for poor physical health-related quality of life,\(^2\) inability to return to work 12 months after hospital discharge,\(^3\) increased health care costs,\(^4\) and subsequent major adverse cardiac events (MACE) and all-cause mortality.\(^5,\!^6\) We recently found that approximately 25% of patients who presented to the emergency department (ED) with a potentially life-threatening medical emergency subsequently developed clinically significant PTSD symptoms 30 days after discharge. The proportion of patients who developed PTSD symptoms was the same regardless of whether they were admitted to the intensive care unit (ICU) or not (i.e., discharged from the ED or admitted to a non–critical care floor), suggesting that a potentially life-threatening event in the ED itself can result in the development of PTSD symptoms.\(^7\)

Perceived threat (conceptualized as a self-measured sense of life endangerment and personal vulnerability)\(^8,\!^9\) has previously been described as a contributor to the development of traumatic injury–induced PTSD (e.g., after motor vehicle crash or military-related trauma).\(^10–12\) The Trauma Recovery Project, a large multicenter epidemiologic study, cites perceived threat to life as a significant predictor of PTSD symptoms among patients experiencing traumatic injury.\(^13\) Similarly, a meta-analysis of risk factors of PTSD found that individuals with increased reports of perceived threat during a traumatic life experience showed higher levels of PTSD symptoms thereafter.\(^11\) Although the relationship between perceived threat and the subsequent development of PTSD symptoms has been well described among patients with external trauma-induced PTSD (rather than somatic/medical), as well as among patients with acute coronary syndrome,\(^14\) this relationship has not been evaluated among patients presenting to the ED with respiratory or cardiovascular instability requiring a potentially life-sustaining intervention. Further, the incidence of PTSD symptoms among patients with respiratory instability in the ED has not been previously reported.

The objective of this preplanned analysis of a prospective cohort study was to test the association between patient-perceived threat during resuscitation in the ED and PTSD symptoms 30 days after discharge among patients presenting to the ED with a potentially life-threatening medical emergency. We hypothesized that perceived threat in the ED is common and an independent predictor of PTSD symptoms 30 days after discharge.

### MATERIALS AND METHODS

#### Study Setting and Population
We performed a preplanned analysis of a prospective cohort study at an academic hospital in the United States (Cooper University Hospital, Camden, NJ). The institutional review board at our institution approved this study, and all subjects provided written informed consent. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.\(^15\)

We included adult patients who were treated for a potentially life-threatening medical emergency, defined as respiratory or cardiovascular instability requiring an acute, potentially life-sustaining intervention in the ED between January and December 2018. Inclusion criteria were 1) adult patients (i.e., age \(\geq 18\) years) and 2) clinician decision to initiate at least one potentially life-sustaining intervention in the ED to manage respiratory or cardiovascular instability: continuous intravenous infusion of a vasoactive agent, insertion of a central venous catheter for volume resuscitation, non-invasive positive pressure ventilation (NPPV), continuous administration of inhaled beta-agonist, insertion of an invasive airway (e.g., supraglottic airway, endotracheal tube), or placement of a thoracostomy tube. Exclusion criteria included 1) Glasgow coma motor scale \(< 6\) (i.e., inability to follow commands) on arrival to ED, 2) traumatic injury as the reason for presenting to the ED, 3) previously diagnosed with PTSD or other severe mental health disorder (i.e., bipolar disorder, schizophrenia, schizoaffective disorder), 5) previously diagnosed with dementia, 6) did not provide informed consent, 7) pregnancy, and 8) prisoner. During the screening process potential subjects were inquired about, and electronic medical records were reviewed for, exclusion criteria.

#### Data Collection
We prospectively assessed patient perception of perceived threat in the ED using a previously validated measurement tool (Table 1),\(^9\) after completion of care in the ED, while the patients were still in the hospital. The individual item scores on the perceived threat
scale were summed to obtain the total perceived threat score, with higher scores indicating greater perceived threat (possible score range = 0 to 21). For each patient, we also recorded comorbid conditions (i.e., Charlson comorbidity index), presenting vital signs in the ED, severity of illness (i.e., Acute Physiologic Assessment and Chronic Health Evaluation [APACHE] II score), and all therapeutic interventions initiated in the ED, as well as ED length of stay and ED crowding using the National Emergency Department Overcrowding Study (NEDOCS) tool.

Outcome Measure

The primary outcome measure was the development of subsequent PTSD symptoms 30 days after discharge, assessed using the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM)-5 (PCL-5; Data Supplement S1, Supplemental Methods, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.7ACEM.7/full)1111, 1387.19,20 The PCL-5 is a well-validated, self-reported measurement tool used to assess the 20 DSM-5 symptoms of PTSD. We administered the PCL-5 via phone. The assessment of PTSD using the PCL-5 via phone has been previously validated and used in clinical research.7,21 All PCL-5 questions were asked in relation to patients’ previous ED visit. The PCL-5 assessments were blinded to all data pertaining to the initial ED visit, specifically the perceived threat scores, and overseen by a clinical psychologist. A 30-day follow-up for administration of the PCL-5 was chosen because PTSD diagnosis requires a 1-month period postevent.22 In addition, PTSD symptoms 30 days after hospital discharge are associated with increased risk for subsequent MACE and all-cause mortality.5,6,23 All data were stored in Research Electronic Data Capture (REDCap), a secure, Web-based application designed to support data capture for research studies,24 and exported into Stata/SE 15.1 for Mac (StataCorp LP) for analysis.

Data Analysis

We displayed categorical data as counts and proportions and continuous data as mean values and standard deviation (SD) or median values and interquartile range (IQR), based on distribution of data. We tested the reliability of the perceived threat measurement tool using Cronbach’s alpha. We tested whether severity of illness (APACHE II score) was associated with perceived threat scores using univariable linear regression analysis. We also compared median (IQR) perceived threat and PCL-5 scores between 1) patients admitted to the ICU versus those discharged or admitted to a non–critical care setting, 2) patients who presented to the ED during a time of ED overcrowding (defined by NEDOCS > 100)18,25 versus no overcrowding, and 3) respiratory instability (i.e., requiring NPPV, continuous administration of inhaled beta-agonist, or placement of an invasive airway in the ED) versus no respiratory instability.

For the primary outcome, we performed multivariable linear regression and selected the covariates a priori26 that are associated with the development of PTSD symptoms after hospitalization. The following covariables were included in the regression model: 1) age,27 2) sex,28 3) ED overcrowding (defined by NEDOCS > 100),18,25 and 4) admission to the ICU (vs. admission to a non–critical care setting or discharge home).29 For the main analyses listwise deletion was used for missing data. We also report results with missing data imputed using multiple imputation by chained equations.30 We performed a post hoc sensitivity analysis using multivariable linear regression adjusting for respiratory instability. We also calculated the absolute mean difference in PCL-5 scores between patients with a low perceived threat score (defined as a perceived threat score less than or equal to the median perceived threat score) compared to patients with a high perceived threat score (defined as a perceived threat score greater than the median perceived threat score).

To further elucidate which aspects of perceived threat had the strongest association with PTSD symptoms at 30 days, we tested the association between the individual perceived threat item scores (Table 1) and PTSD symptoms at 30 days using univariable linear
regression analyses. For all models, conservative robust standard errors were used to reduce the risk of type I error.

**Sample Size Calculation**
Assuming 1) $\alpha = 0.05$, 2) power $= 0.08$, 3) SD of the PCL-5 of 15, and 4) SD of the perceived threat scale of 6, we determined that to detect the alternative hypothesis $\beta = 0.71$ (for a two-tailed test against the null hypothesis $\beta = 0$) for the association between perceived threat in the ED and PTSD symptoms at 30 days, we would require 92 total subjects.31

**RESULTS**
A total of 113 subjects were enrolled and 99 completed follow-up (study flow diagram previously published).7 Patients included in the primary analysis had similar characteristics compared to those lost to follow-up (comparisons previously published).7 Table 2 displays baseline data at the time of presentation to the ED as well as ED and hospital characteristic for all subjects.7 The median (IQR) ED APACHE II score was 12 (9 to 15). The perceived threat measurement tool had good reliability (Cronbach’s $\alpha = 0.86$). Ninety-eight percent of patients reported some degree of perceived threat. The median (IQR) perceived threat score was 12 (6 to 17). The distributions of the total perceived threat scores, as well as the individual item scores are displayed in Data Supplement S1, Figures S1–S8. Seven patients were missing a response to a perceived threat question. We did not find severity of illness in the ED (APACHE II score) to be predictive of the degree of perceived threat in the ED ($\beta = 0.15$, 95% confidence interval [CI] = $-0.04$ to 0.33).

Seventy-two percent of patients reported at least one positive PTSD symptom at 30 days (defined as a score of 2 or more on at least one PCL-5 question), and 25% reported clinically significant PTSD symptoms (defined as scored 2 or more on at least one B item [questions 1–5], one C item [questions 6 and 7], two D items [questions 8–14], or two E items [questions 15–20] or a total score greater than 32).19,20 Among the entire cohort the median (IQR) PCL-5 score was 7 (0 to 30). The median (IQR) perceived threat scores (12 [5 to 17] vs. 14 [7 to 18]) and PCL-5 scores (6 [1 to 20] vs. 8 [0 to 36]) were similar between patients admitted to the ICU and those admitted to a non–critical care setting or discharged home as well as among those who presented to the ED during a period of ED overcrowding versus no overcrowding (perceived threat score 12 [5 to 18] vs. 13 [8 to 17] and PCL-5 score 6 [0 to 27] vs. 9 [2 to 33], respectively). Patients with respiratory instability had higher median (IQR) perceived threat scores (16 [9 to 18] vs. 9 [6 to 14]) and PCL-5 scores (10 [2 to 40] vs. 3 [0 to

<table>
<thead>
<tr>
<th>Table 2: Patient Characteristics</th>
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<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>White/Caucasian</td>
</tr>
<tr>
<td>Black/African American</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Hispanic Ethnicity</td>
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<tr>
<td>Preexisting comorbidities</td>
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<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Known coronary artery disease</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Malignancy</td>
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<tr>
<td>Renal insufficiency</td>
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<tr>
<td>Pulmonary disease</td>
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<tr>
<td>Cerebral vascular disease</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Charlson comorbidity score</td>
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<tr>
<td>Presenting ED vital signs</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
</tr>
<tr>
<td>NEDOCS at time of arrival*</td>
</tr>
<tr>
<td>ED overcrowding at time of arrival*</td>
</tr>
<tr>
<td>Medical emergency</td>
</tr>
<tr>
<td>Respiratory</td>
</tr>
<tr>
<td>NPPV</td>
</tr>
<tr>
<td>Continuous beta-agonist</td>
</tr>
<tr>
<td>Invasive airway</td>
</tr>
<tr>
<td>Tube thoracostomy</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>APACHE II score in the ED</td>
</tr>
<tr>
<td>ED length of stay (hours)</td>
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<tr>
<td>Disposition from the ED</td>
</tr>
<tr>
<td>Discharge home</td>
</tr>
<tr>
<td>Medical floor/telemetry</td>
</tr>
<tr>
<td>Catheterization laboratory</td>
</tr>
<tr>
<td>ICU</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
</tr>
</tbody>
</table>

Data are reported as mean (±SD), n (%), or median (IQR).
APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; ICU = intensive care unit; IQR = interquartile range; NEDOCS = National Emergency Department Overcrowding Study; NPPV = noninvasive positive pressure ventilation.
* NEDOCS tool score > 100.
found perceived threat in the ED to be common and an independent predictor of PTSD symptoms at 30 days. Specifically, we found feelings of helplessness and fear in the ED to have the strongest associations with PTSD symptoms. We found patients who present to the ED with respiratory instability had greater perceived threat scores in the ED as well as greater PTSD symptoms at 30 days than patients who presented without respiratory instability. These results suggest that patients who present to the ED with respiratory distress may be a previously unidentified population at high risk for subsequent development of PTSD symptoms.

Our finding that perceived threat is associated with PTSD symptoms among ED patients with a potentially life-threatening medical emergency is consistent with previous literature. Perceived threat has been demonstrated to be a predictor of PTSD symptoms among burn patients as well as patients with acute coronary syndrome. Perceived threat has also been demonstrated to have a stronger association with the development of cognitive symptoms that are part of PTSD symptomatology (i.e., intrusive thoughts and avoidance) among oncology patients, than actual cancer stage. Among traumatic injury victims, perceived threat has been found to be an integral component in the development of PTSD. Specifically, perceived threat is associated with peritraumatic dissociation (i.e., alteration in time or place with reported feelings of depersonalization, altered perceptions of pain, feeling disconnected, or tunnel vision), which in turn is an independent predictor of PTSD. Further research is required to test whether the association between perceived threat in the ED and PTSD symptoms at 30 days among patients with nontraumatic medical emergencies is mediated by peritraumatic dissociation. In addition, prior research in patients with acute coronary syndrome suggests that perceived threat in the ED predicts PTSD symptoms at 30 days primarily in patients who continue to report ongoing body-focused worry in the month after discharge, so future research should assess enduring somatic threat perceptions in these patients.

There are currently large ongoing studies evaluating PTSD among traumatic injury survivors (AURORA study, https://www.med.unc.edu/ittr/aurora-study) as well as patients with acute stroke, acute coronary syndrome, and post–cardiac arrest syndrome (REActions to Acute Care and Hospitalization [REACH] study, NCT03605693). Our results expand upon the REACH study as it identifies an additional cohort of subjects who are also at risk for a high degree of

### DISCUSSION

We performed a prospective cohort study and tested the association between patient-perceived threat in the ED and the development of PTSD symptoms 30 days after discharge among patients presenting to the ED with a potentially life-threatening medical emergency. We found perceived threat in the ED to be common and an independent predictor of PTSD symptoms at 30 days.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression Coefficients (β)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-perceived threat score</td>
<td>0.79</td>
<td>0.15 to 1.42</td>
</tr>
<tr>
<td>Female</td>
<td>3.34</td>
<td>-4.38 to 11.05</td>
</tr>
<tr>
<td>Age</td>
<td>-0.12</td>
<td>-0.41 to 0.17</td>
</tr>
<tr>
<td>Admission to the ICU</td>
<td>-1.47</td>
<td>-8.75 to 5.81</td>
</tr>
<tr>
<td>ED overcrowding</td>
<td>-1.85</td>
<td>-9.63 to 5.92</td>
</tr>
</tbody>
</table>

ICU = intensive care unit; PCL-5 = Posttraumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition.
perceived threat in the ED and the subsequent development of PTSD symptoms.\textsuperscript{27} Our findings are also consistent with initial REACH study results, which found an association between perceived threat in the ED and the PCL at 1 month ($\beta = 0.71$) among patients with acute coronary syndrome.\textsuperscript{31} Further, these ongoing studies are evaluating interventions applied after the psychologically traumatic event has already occurred. Our findings support future research aimed at identifying interventions that can be implemented in the ED during acute resuscitation in an effort to reduce perceived threat and prevent psychological trauma and subsequent PTSD development, as opposed to attempting to attenuate or treat the symptoms after the psychologically traumatic event has already occurred.

Our results, demonstrating high perceived threat among patients with respiratory instability, may be intuitive to some extent. The symptom of dyspnea and the sense of suffocation can be a terrifying experience, triggering anxious arousal, which has the effect of further magnifying respiratory symptoms that can induce panic.\textsuperscript{38–40} Patients with acute respiratory distress often have catastrophic thinking and overperception of symptoms, which can result in a high anxiety state as well as worsening respiratory symptoms.\textsuperscript{41} For example, dyspnea-induced panic has been shown to increase minute ventilation above actual physiologic demand.\textsuperscript{42} In a multivariable linear regression analysis, we found both perceived threat and respiratory instability to be independently predictive of PTSD symptoms at 30 days. These results suggest that the higher perceived threat associated with respiratory instability does not account fully for the greater PTSD symptoms among this cohort. It may be possible that respiratory distress results in a higher degree of peri-traumatic disassociation or a more pronounced ongoing somatic threat perception after discharge; however, further research is required to test these hypotheses.

LIMITATIONS

We acknowledge that this study has several limitations to consider. First, given its observational design, this study can only describe associations and cannot infer causation. Second, there is heterogeneity among previous methods used to measure perceived threat. In addition, we are unaware of any objective physiologic parameters, which could be measured in this patient population that have previously been shown to have a correlation with perceived threat. Therefore, we used a previously validated measurement tool, which to the best of our knowledge is the only perceived threat scale that has undergone extensive psychometric testing.\textsuperscript{9} In addition, we prospectively measured patient degree of perceived threat while patients were still in the hospital, as opposed to at the time of PTSD assessment, in an effort to reduce recall bias. We also found the perceived threat measurement tool to have good internal reliability among our cohort. Third, we based our definition of a potentially life-threatening medical emergency on interventions initiated by the treating clinician in the ED. Thus, it is possible that had the intervention not been performed in the ED that some patients may have survived regardless (i.e., not truly a life-threatening diagnosis). Therefore, we are unable to state whether or not patients had an actual life-threatening diagnosis. However, it is the perception of life threat that likely leads to patient-perceived threat rather than actual life threat. Fourth, although the PCL-5 is a well-validated measurement tool that is frequently used in research to assess PTSD symptoms,\textsuperscript{20,43,44} it is a screening tool and not a diagnostic test for PTSD.

CONCLUSIONS

In summary, we found patient-perceived threat in the ED to be common and an independent predictor of posttraumatic stress disorder symptoms at 30 days. In addition, we found that patients who present to the ED with respiratory instability to be at high risk for the development of posttraumatic stress disorder symptoms. Future research is warranted to test if interventions to reduce perceived threat in the ED can reduce the development of posttraumatic stress disorder symptoms.

References


Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13877/full

Data Supplement S1. Supplemental material.
Analysis of Partial Thromboplastin Times in Patients With Pulmonary Embolism During the First 48 Hours of Anticoagulation With Unfractionated Heparin

Christiana K. Prucnal, BSN, RN-BC, Paul S. Jansson, MD, MS, Erin Deadmon, Rachel P. Rosovsky, MD, MPH, Hui Zheng, PhD, and Christopher Kabrhel, MD, MPH

ABSTRACT

Objective: The objective was to determine the proportion of patients with pulmonary embolism (PE) treated with unfractionated heparin (UFH) who achieved therapeutic activated partial thromboplastin time (aPTT) values within 48 hours of treatment.

Methods: Retrospective analysis of a PE response team (PERT) database was performed at a large, urban, academic teaching hospital. Inclusion criteria were adult patients with acute PE for whom the PERT was consulted and who received anticoagulation (AC) with UFH according to guideline standard dosing. aPTT values during 6-hour time periods during the first 48 hours of AC were collected and analyzed.

Results: A total of 505 patients met inclusion criteria. For patients receiving a bolus and infusion of UFH, the proportions (95% confidence interval [CI]) of patients in the therapeutic range were 19.0% (14.2% to 25.0%) at 12 hours, 26.3% (26.3% to 33.1%) at 24 hours, 28.3% (22.0% to 35.4%) at 36 hours, and 28.4% (20.8% to 37.5%) at 48 hours. For titrated infusion only, the proportions (95% CIs) of patients were 23.3% (16.2% to 32.3%) at 12 hours, 41.4% (31.6% to 51.9%) at 24 hours, 37.0% (26.8% to 48.5%) at 36 hours, and 42.1% (30.2% to 55.0%) at 48 hours. No patient had all therapeutic aPTTs.

Conclusions: The majority of patients with acute PE spend most of their first 48 hours outside of the therapeutic range of AC when treated with guideline standard dosing of UFH. Over half of the patients fail to achieve any therapeutic PTT level within 24 hours of UFH initiation, and no patient had all therapeutic aPTTs. Future research should focus on identifying factors associated with achieving therapeutic AC with UFH.
BACKGROUND

Pulmonary embolism (PE) is relatively common, with an annual incidence between 75 and 269 cases per 100,000 persons. PE can range in severity from asymptomatic to life-threatening, with a mortality rate from 20% to upwards of 40% in those with hemodynamic instability.

The mainstay of treatment for symptomatic PE is pharmacologic anticoagulation (AC). However, some patients with more high-risk PEs may require advanced interventions such as thrombolytic therapy, surgical embolectomy, or even extracorporeal membrane oxygenation (ECMO). Because of the complexity of treatment options for higher-risk PEs, many institutions have developed PE response teams (PERTs) to rapidly coordinate teams of specialists to advise and coordinate these therapies.

Importance

While long-term AC can be achieved with oral agents, AC in the acute phase is typically achieved with parenteral heparinoids. Because of its short half-life and availability of a reliable reversal agent, unfractionated heparin (UFH) may be used when a percutaneous or surgical intervention is being considered and for patients at high risk of bleeding.

The dosing of UFH is weight-based: the standard dose is an intravenous 80 unit/kg bolus followed by an infusion started at 18 units/kg/hour, titrated to a target activated partial thromboplastin time (aPTT) of 1.5 to 2.5 times the control range or an anti-Xa level of 0.3 to 0.7 μ/mL. Although this “standard dose” has been developed, UFH has long been known to have unpredictable pharmacokinetics and thus far only one small study (n = 45) has explored the efficacy of this standard dose in patients with acute PE, finding only 22% of aPTT values within the reference range.

Goals of This Investigation

Therefore, given the expansion of PERTs worldwide and the unpredictable pharmacokinetics of UFH, we sought to determine the proportion of PERT patients at our institution treated with UFH who achieved a therapeutic aPTT within 48 hours of UFH initiation.

METHODS

We enrolled all patients for whom the Massachusetts General Hospital (MGH) PERT was activated between October 22, 2012, and April 1, 2017. Fully described elsewhere, the MGH PERT is a multidisciplinary team of physicians who can be activated by any treating clinician. A PERT representative responds to gather clinical information; the PERT then meets virtually to review clinical information and provide treatment recommendations to the referring clinician.

From among the MGH PERT patients, we included those who were treated with a standard dose of UFH and had at least one aPTT reported after UFH initiation. Demographic, comorbidity, diagnostic, treatment, and outcome data are prospectively entered into a registry for all patients for whom PERT is activated. For this analysis, a trained research coordinator experienced with the PERT registry and electronic medical review performed chart abstraction for anticoagulant dose and all aPTT values within 48 hours after initiation of AC therapy.

Measurements

Dosing with UFH was coded based on the order for UFH placed at initiation of AC. We considered two dosing regimens to be “standard dosing”: A) “bolus plus titrated infusion” if a bolus dose of 80 units/kg plus a continuous titrated infusion starting at 18 units/kg/hour was ordered and B) “titrated infusion only” if only a continuous titrated infusion of 18 units/hour was ordered (a commonly used dosing strategy for patients thought to have a high risk of bleeding by the treating team). Ordering of the heparin was made via a templated protocol embedded in the electronic medical record (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Heparin Protocol</th>
<th>Bolus Dose (U/kg)</th>
<th>Rate Change (U/kg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial bolus</td>
<td>80</td>
<td>—</td>
</tr>
<tr>
<td>Subsequent aPTT (seconds)*</td>
<td></td>
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</tr>
<tr>
<td>&lt;40</td>
<td>60</td>
<td>+3</td>
</tr>
<tr>
<td>40–49.9</td>
<td>30</td>
<td>+2</td>
</tr>
<tr>
<td>50–59.9</td>
<td>—</td>
<td>+1</td>
</tr>
<tr>
<td>60–80</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>80.1–100</td>
<td>—</td>
<td>—2</td>
</tr>
<tr>
<td>&gt;100</td>
<td>Hold dose for 60 minutes</td>
<td>—3</td>
</tr>
</tbody>
</table>

aPTT = activated partial thromboplastin time.

*Per protocol, an aPTT is drawn every 6 hours after the bolus and any dose adjustments. If aPTT result is within the reference range for two consecutive 6-hour measurements, further aPTT measurement can be spaced to every 12 hours.
aPTT values were grouped by 6-hour time periods after the initiation of AC (e.g., the “12-hour” aPTT cohort included aPTT values drawn from 9 to 15 hours after initiation of AC). The initiation of AC was defined as the order start time for UFH in the electronic medical record. A baseline aPTT was not required by the protocol.

Outcomes

Our primary outcome was the proportion of patients with a therapeutic aPTT value during each 6-hour time period. A therapeutic aPTT was defined as a value of 60 to 80 seconds on the institutional aPTT reagent (Platelin L, Diagnostica Stago, Inc, Asnieres, France; normal range = 22–35 seconds), which corresponds to an anti-Xa level of 0.3-0.7 µ/mL (Dr. Elizabeth Van Cott, personal communication, Aug 27, 2018).

For patients with more than one aPTT value in a given 6-hour time period, the first therapeutic value was selected for analysis. If there was no therapeutic value, the first aPTT value reported was used. Patients treated with nonstandard dosing regimens were excluded, and once patients were switched to another form of AC they were removed from further analysis.

Data Analysis

We calculated proportions and 95% confidence intervals (CIs) based on the number of patients with an aPTT reported during that 6-hour time period. Patients without an aPTT value within a given 6-hour window were excluded from that denominator. We stratified our analysis according to whether patients were treated with “bolus plus titrated infusion” or “titrated infusion only.” We also calculated the cumulative proportion of patients with any therapeutic aPTT value and the cumulative proportion of patients who had all therapeutic aPTT values. All analyses were performed using SAS version 9.4.

Table 2: Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall % (n)</th>
<th>Bolus and Infusion</th>
<th>Infusion Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>66 (55–76)</td>
<td>66 (53.5–76.0)</td>
<td>67 (58.0–76.0)</td>
</tr>
<tr>
<td>Gender, female</td>
<td>47.1% (238)</td>
<td>46.0% (160)</td>
<td>49.7% (78)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>79.6% (402)</td>
<td>79.6% (277)</td>
<td>79.6% (125)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>8.7% (44)</td>
<td>9.2% (32)</td>
<td>7.6% (12)</td>
</tr>
<tr>
<td>Asian</td>
<td>2.4% (12)</td>
<td>2.3% (8)</td>
<td>2.6% (4)</td>
</tr>
<tr>
<td>American Indian or Pacific Islander</td>
<td>0.2% (1)</td>
<td>0.3% (1)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>3.0% (15)</td>
<td>3.2% (11)</td>
<td>2.6% (4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.1% (31)</td>
<td>5.5% (19)</td>
<td>7.6% (12)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (IQR)</td>
<td>29.3 (26.2–35.7)</td>
<td>29.0 (26.5–32.7)</td>
<td>29.4 (24.4–36.3)</td>
</tr>
<tr>
<td>CCI, median (IQR)</td>
<td>2 (0–4)</td>
<td>1.5 (0–4)</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>PE severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saddle PE</td>
<td>17.4% (88)</td>
<td>18.1% (63)</td>
<td>15.9% (25)</td>
</tr>
<tr>
<td>Right heart strain on CT</td>
<td>46.9% (215)</td>
<td>49.7% (142)</td>
<td>63.5% (73)</td>
</tr>
<tr>
<td>Hemodynamic collapse</td>
<td>7.9% (40)</td>
<td>7.5% (26)</td>
<td>8.9% (14)</td>
</tr>
<tr>
<td>Massive PE</td>
<td>28.3% (127)</td>
<td>26.6% (84)</td>
<td>32.3% (43)</td>
</tr>
<tr>
<td>Right heart strain on echo</td>
<td>21.4% (108)</td>
<td>22.4% (78)</td>
<td>19.1% (30)</td>
</tr>
<tr>
<td>Elevated troponin level</td>
<td>55.3% (252)</td>
<td>54.4% (174)</td>
<td>57.4% (78)</td>
</tr>
<tr>
<td>Interventions received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic thrombolysis</td>
<td>4.0% (20)</td>
<td>2.9% (10)</td>
<td>6.4% (10)</td>
</tr>
<tr>
<td>Catheter-based Intervention</td>
<td>5.9% (30)</td>
<td>6.6% (23)</td>
<td>4.5% (7)</td>
</tr>
<tr>
<td>Surgical embolectomy</td>
<td>2.0% (10)</td>
<td>2.3% (8)</td>
<td>1.3% (2)</td>
</tr>
<tr>
<td>ECMO</td>
<td>1.4% (7)</td>
<td>0.6% (2)</td>
<td>3.2% (5)</td>
</tr>
<tr>
<td>IVC filter</td>
<td>5.0% (25)</td>
<td>4.3% (15)</td>
<td>6.4% (10)</td>
</tr>
<tr>
<td>Outcome (30 day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>5.7% (19)</td>
<td>5.7% (14)</td>
<td>5.6% (5)</td>
</tr>
<tr>
<td>Rethrombosis</td>
<td>3.9% (13)</td>
<td>4.5% (11)</td>
<td>2.2% (2)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3.0% (10)</td>
<td>2.9% (7)</td>
<td>3.3% (3)</td>
</tr>
</tbody>
</table>

CCI = Charlson Comorbidity Index; ECMO = extracorporeal membrane oxygenation; IVC = inferior vena cava; IQR = interquartile range.
<table>
<thead>
<tr>
<th>Dosing Type</th>
<th>Hours After Initiation of Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td><strong>Subtherapeutic (aPTT &lt; 60)</strong></td>
<td></td>
</tr>
<tr>
<td>Bolus and infusion</td>
<td>51.3%</td>
</tr>
<tr>
<td></td>
<td>45.3%–57.4% (137/267)</td>
</tr>
<tr>
<td>Infusion only</td>
<td>48.1%</td>
</tr>
<tr>
<td></td>
<td>39.7%–56.6% (63/131)</td>
</tr>
<tr>
<td><strong>Therapeutic (aPTT 60–80)</strong></td>
<td></td>
</tr>
<tr>
<td>Bolus and infusion</td>
<td>13.9%</td>
</tr>
<tr>
<td></td>
<td>10.2%–18.5% (37/267)</td>
</tr>
<tr>
<td>Infusion only</td>
<td>14.5%</td>
</tr>
<tr>
<td></td>
<td>9.5%–21.5% (19/131)</td>
</tr>
<tr>
<td><strong>Supratherapeutic (aPTT &gt; 80)</strong></td>
<td></td>
</tr>
<tr>
<td>Bolus and infusion</td>
<td>34.8%</td>
</tr>
<tr>
<td></td>
<td>29.4%–40.7% (83/267)</td>
</tr>
<tr>
<td>Infusion only</td>
<td>37.4%</td>
</tr>
<tr>
<td></td>
<td>29.6%–45.9% (49/131)</td>
</tr>
</tbody>
</table>

aPTT = activated partial thromboplastin time.
Recognizing that patients treated with systemic or catheter-directed thrombolysis, surgical embolectomy, or ECMO may have their AC discontinued or adjusted during the intervention, we performed a sensitivity analysis excluding all patients who were treated with any of those modalities. This study was approved by the MGH Institutional Review Board (Protocol 2016P000179).

RESULTS

From October 22, 2012, to April 1, 2017, a total of 716 patients with PE were enrolled in the PERT registry, 532 of whom received AC with UFH. Four patients did not have any aPTT values recorded and were therefore excluded, as were an additional 23 patients who were treated with a nonstandard heparin dose, leaving 505 patients eligible for analysis.

Table 2 describes the included population. Briefly, the median (interquartile range [IQR]) age was 66 (55–76) years and 238 (47%) were female. The cohort was primarily white (n = 402, 79.5%), and the median (IQR) BMI was 29 (26-35) kg/m². Approximately half of the patients (n = 438, 47%) had evidence of right heart strain on CT pulmonary angiography. Advanced interventions were rare with 4.0% (20 patients) undergoing systemic thrombolysis, 5.9% (30) catheter-based interventions, 2% (10) surgical embolectomy, and 1.4% (7) ECMO.

Table 3 shows complete percentages, CIs, and numbers of patients at each measured time point in both dosing cohorts. For those patients anticoagulated with a bolus followed by titrated infusion (n = 348), Figure 1 shows that less than half of all patients who had an aPTT reported had an aPTT in therapeutic range during any 6-hour period. The percentages of patients who had a therapeutic aPTT were 13.9, 19.0, 25.8, 34.2, 34.9, and 28.4% at 6, 12, 18, 24, 30, 36, and 48 hours, respectively. The percentages of patients who had a subtherapeutic aPTT were 51.3, 59.0, 52.0, 54.8, 48.2, 55.9, 48.8, and 60.6%, while the percentages of patients who had a supratherapeutic aPTT were 34.8, 22.0, 22.0, 18.8, 17.7, 15.9, 16.3, and 11.0% for the same time periods.

The proportion of patients who maintained all therapeutic aPTT values was poor. Only 1.3% of patients in the bolus group and 0.7% in the infusion only cohort had entirely therapeutic aPTT values for the first 12 hours, and no patient had all therapeutic aPTT values thereafter.

Of the patients who spent time outside of the therapeutic range, there was little consistency. In the bolus and continuous infusion cohort, 0.6 and 0% of patients had entirely supratherapeutic values for the first 24 and 48 hours, respectively, while 3.2 and 0% were entirely subtherapeutic for the same time periods. A total of 21.5% of patients (75/349) had both a supratherapeutic and a subtherapeutic aPTT during the first 24 hours, and 36.4% (127/349) had both during the first 48 hours.

For the continuous infusion-only cohort, the results were comparable with 0.6 and 0% entirely supratherapeutic for the first 24 and 48 hours and 1.9 and 0.6% entirely subtherapeutic, respectively. A total of 26.6% of patients (42/158) had both a supratherapeutic and a subtherapeutic aPTT during the first 24 hours, and 44.3% (70/158) had both during the first 48 hours.

Moreover, patients often crossed between groups. For example, in the bolus and infusion cohort, between the 6-hour interval and the 12-hour interval, 31.3% (10/32) patients moved from therapeutic to supratherapeutic and 43.8% (14/32) moved therapeu tic to subtherapeutic. A total of 31.6% (31/98) moved from supratherapeutic to therapeutic and 12.2% (15/123) moved subtherapeutic to therapeutic. Together, these results suggest significant variability in aPTT values throughout the first 48 hours of treatment.

Figure 3 and Figure 4 show the distribution of aPTT values at each time point for the bolus and infusion and infusion-only cohort, respectively. In the bolus and infusion cohort, the mean time from 80 ranged from 17.3 to 42.5 seconds for supratherapeutic values and 13.9 to 18.7 seconds from 60 for subtherapeutic values in each time period. In the infusion only
cohort, the mean time from 80 ranged from 11.5 to 42 second for supratherapeutic values and 12.1 to 18.1 seconds from 60 for subtherapeutic values in each time period.

Figure 5 shows the cumulative proportion of patients who had achieved at least one therapeutic aPTT. Among patients treated with a bolus plus infusion, the cumulative percentage with at least one therapeutic aPTT measured was 13.9, 22.8, 32.4, 40.6, 48.7, 53.1, 56.2, and 57.4% at 6, 12, 18, 24, 30, 36, 42, and 48 hours, respectively. Among patients treated with a titrated infusion only, the cumulative percentage with at least one therapeutic aPTT measured was 14.5, 28.2, 38.0, 50.7, 53.6, 58.2, 60.1, and 62.1% for the same time periods. Analysis of the data excluding patients who underwent systemic or catheter-directed thrombolysis, surgical embolectomy, or ECMO produced results that were similar to the original analysis (data not shown).

LIMITATIONS

Our study has several potential limitations. We report data from a single institution, so local factors may limit the generalizability of this study. However, we restricted our analysis to patients treated with a standard UFH dosing regimen, supported by published guidelines.4–6 Our results are also similar to previously published work showing significant time outside of the therapeutic range.1,9,20

Furthermore, there are many available aPTT assays that may have different test characteristics between institutions. We used an institutional reference range of 60–80 seconds, which may appear to be narrower than what is considered therapeutic at other institutions, but was chosen because it was calibrated against an anti-Xa assay. Although the aPTT assay has multiple limitations and may not be the most precise test to monitor the efficacy of heparin AC, it is the most widely used assay in clinical practice.22,23

In addition, we used the heparin order time as a proxy for the initial medication administration time due to limitations in the electronic medical record. This may falsely increase the time to therapeutic range, although it is unlikely to represent a significant delay overall.

It should be noted that the number of aPTT samples decreases throughout the duration of the study, which may bias the results. It is possible that the aPTTs were spaced out as the patients became therapeutic, as allowed by our hospital’s protocol. However, this could only apply to a maximum of 28% of the patients in the cohort (assuming that every patient therapeutic at hour 36 [28.2% overall] was also therapeutic at hour 42 [34.9%]). This seems improbable given the variability seen in the study. Given the high-risk nature of this cohort very few of our patients were discharged within the first 48 hours of therapy and the 30-day mortality was less than 6%, so we do not feel that this explains our findings. The most likely reason for the decrease in the number of aPTTs checked is that patients were switched to other modes of AC when invasive management was not recommended by PERT. The need to switch patients to a more reliable anticoagulant only strengthens our conclusions.

We also considered all time outside the reference range equally, so values close to the therapeutic cutoff were considered equivalent to those far from the cutoff. We recognize that an aPTT that is slightly above the reference range may aid in AC without significantly increasing the bleeding risk and may be less harmful than a subtherapeutic aPTT during the acute presentation of PE. However, given the fact that the majority of out of range values in our study were subtherapeutic, we feel that our data support a conclusion of inadequate AC in a large proportion of cases. Finally, we appreciate that there may be selection bias insofar as the patients in our study were seen and evaluated by a PERT and thus likely represent a sicker and more complex subset of patients with PE. Importantly, these are precisely the patients who are most at risk of complications from subtherapeutic AC.

DISCUSSION

In this analysis of 505 patients with acute PE, only a minority of patients treated with UFH had a therapeutic aPTT during the first 48 hours of AC and the majority of patients were subtherapeutic. The proportion of patients in therapeutic range was lowest at 6 hours (14%) and highest at 42 hours (35%). Receiving standard UFH dosing, approximately 40% of patients failed to reach the therapeutic range in the first 48 hours of AC. In fact, not until 36 hours after the initiation of UFH did more than 50% of patients have at least one therapeutic aPTT. There were no patients who had all aPTT values within the therapeutic range during the first 48 hours of UFH therapy. Results for a second commonly used dosing strategy
for patients at high risk of bleeding (e.g., postoperative PE), a titrated UFH infusion without a loading bolus, were similar. These findings indicate that the majority of patients who are treated with UFH for PE spend most of the first 48 hours of AC out of the therapeutic range and many patients fail to achieve therapeutic AC at any point in the first 2 days of treatment.

Therapeutic AC is the cornerstone of acute PE management.4,5,24 It is therefore critically important
Figure 3 Distribution of aPTT points for each 6-hour time period in the bolus and infusion cohort. The yellow and grey solid lines represent the upper and lower bounds of the therapeutic range, respectively. The blue line represents the mean time from the upper limit of the therapeutic range while the orange represents the mean time from the lower limit of the therapeutic range. Each colored dot represents an aPTT value. aPTT = activated partial thromboplastin time.

Figure 4 Distribution of aPTT points for each 6-hour time period in the infusion-only cohort. The yellow and grey solid lines represent the upper and lower bounds of the therapeutic range, respectively. The blue line represents the mean time from the upper limit of the therapeutic range while the orange represents the mean time from the lower limit of the therapeutic range. Each colored dot represents an aPTT value. aPTT = activated partial thromboplastin time.
that the chosen method of AC is both reliable and effective in clinical practice. Several studies have found a mortality benefit to prompt diagnosis and early AC in PE, reinforcing the importance of effective AC.25–27

Adding to the importance of these data is the increasing prevalence of PERTs throughout the United States and globally. PERTs provide rapid, multidisciplinary care for patients with acute PE. Among PERT patients, treatment with UFH is often clinically justified by the potential need for advanced treatment, since it can be discontinued rapidly in advance of possible thrombolysis or surgery. However, PERT patients are also the highest risk PE patients for whom early and effective AC is most important. However, even among our PERT patients, only about 10% of underwent advanced treatment, mostly with catheter-directed thrombolysis. It is therefore likely that very few PE patients in general practice will actually require UFH for the express purpose of “turning it off,” and given the results of our study, we believe that nearly all patients would be better treated with an alternative pharmacologic agent.

There are several potential reasons for our findings. Despite our hospital’s use of electronic order entry, which encourages standard dosing, treatment with UFH is complex and requires frequent monitoring and dose adjustments. With the average patient taking nearly 36 hours to reach a therapeutic level, the data suggest that at least five dosing adjustments are made, introducing multiple opportunities for error, including in assay measurement, results reporting, and medication administration and titration. Because of the need for frequent laboratory testing and dose adjustments, heparin has been labeled as a “high-risk” drug, having been cited in numerous patient safety incidents.28

In addition, thrombus burden associated with clinically significant PE can be substantial and heparin resistance may be present, so standard dosing may be inadequate. Regardless of the cause, our data support that current dosing of UFH leaves many patients with PE under- or overanticoagulated and, therefore, at risk for adverse clinical outcomes.

Further research should analyze the factors that lead to aPTT values within the reference range and should compare the effectiveness of UFH to other anticoagulant medications, such as that of low-molecular-weight heparin (LMWH), which a recent Cochrane review found may be superior to UFH.29 Since UFH is often used for patients in whom an intervention or reversal is anticipated, the proportion of patients who actually receive intervention or reversal should be studied and the use of LMWH in these patients should be explored. Furthermore, outcome data should be assessed to determine whether time spent in the therapeutic range affects morbidity and mortality.

CONCLUSIONS

In conclusion, in our analysis of 505 patients treated with the standard dosing of unfractionated heparin for acute pulmonary embolism, most patients failed to reach therapeutic anticoagulation within the first 48 hours of therapy. Patients were primarily
subtherapeutic during the 6-hour time periods we studied, and no patient achieved a therapeutic activated partial thromboplastin time within 6 hours and maintained that therapeutic level thereafter. The administration of unfractionated heparin in the treatment of acute pulmonary embolism needs to be revisited.

We thank Nicholas Giordano and Blair Parry for administrative support of this work. We also thank the members of the MGH PERT team for the inspiration to explore this line of research and for their collaboration and dedication in caring for some of our most vulnerable patients.

References

Adverse Events from Emergency Physician Pediatric Extremity Radiograph Interpretations: A Prospective Cohort Study

Faisal Al-Sani, MD1, Soni Prasad2, Jyoti Panwar, MD3, Jennifer Stimec, MD4, Arash Khosroawshahi, MD2, Trent Mizzi, MD2, Mark Camp, MD, MSc5, Keith Colaco2, Adam Kramer, MSc6, and Kathy Boutis, MD, MSc7

ABSTRACT

Objectives: We determined how often emergency physician pediatric musculoskeletal (MSK) radiograph interpretations were discordant to that of a radiologist and led to an adverse event (AE). We also established the variables independently associated with this outcome.

Methods: This prospective cohort study was conducted in an urban, tertiary care children’s emergency department (ED). We enrolled children who presented to an ED with an extremity injury and received radiographs. ED physicians documented their radiograph interpretation, which was compared to a radiology reference standard. Patients received telephone follow-up and had institutional medical records reviewed in 3 weeks. An AE occurred if there were clinical sequelae and/or repeat health care visits due to a delay in correct radiograph interpretation.

Results: We enrolled 2,302 children (mean ± SD age = 9.0 [4.4] years; 1,288 (56.0%) male). Of these, 180 (7.8%; 95% confidence interval = 6.8 to 9.0) ED physician discordant interpretations resulted in an AE. Specifically, there were no negative clinical outcomes; however, relative to cases diagnosed correctly at the index ED, patients whose fracture was not initially identified encountered 77.2% more subsequent ED visits, while those falsely diagnosed with a fracture experienced 41.5% additional orthopedic clinic visits. Odds of an ED discrepant interpretation was significantly higher if a physician’s pretest probability of a fracture was ≤ 20% versus > 20% (adjusted odds ratio [aOR] = 1.6), patient’s pain score was ≤ 2 versus > 2 (aOR = 1.6), and injury was located in a joint versus other location (aOR = 1.7).

Conclusions: Emergency physician discordant pediatric MSK radiograph interpretations that resulted in an AE occurred with regular frequency in a pediatric ED setting. AEs were primarily an increase in subsequent health care visits. Importantly, a low clinical suspicion for a fracture or injury located in the joint were risk factors for ED physician discordant interpretations.

Pediatric extremity injuries are a common presenting complaint to emergency departments (EDs),1 and radiographs are often ordered to determine the extent of injury. ED physicians are tasked with interpretation of these extremity radiographs and an appropriate initial diagnosis determines management, minimizing morbidity and long-term dysfunction. However, pediatric musculoskeletal (MSK) images may be particularly
challenging for ED physicians to interpret given the physician needs to be aware of developmental anatomy as the child grows, which includes growth plates and ossification centers.2 Previous research has reported diagnostic error rates of pediatric MSK radiographs ranging from 5% to 15%.3,4 These errors may also have medicolegal consequences; pediatric fracture errors in urgent and emergent care settings have been reported as the third most common cause of lawsuits and amounted to third largest amount of dollars paid out to settle malpractice claims in the United States.5

Given the frequency of pediatric MSK injuries, even a small percent of interpretation errors may have significant consequences for patients and health care systems. To date, research aimed to establishing the frequency of pediatric MSK interpretation errors in the ED is limited. Studies often included all types of pediatric radiograph images or include a mix of adult and pediatric radiographs, resulting in a relatively small sample of pediatric MSK radiographs.6–20 Furthermore, most research to date in this area was conducted using a retrospective design, which may be prone to unstandardized methods of recording diagnostic interpretations and result in incorrect estimates. The published estimates to date also emphasize ED physician interpretation errors that miss a fracture/dislocation (false negatives) and have excluded the errors that occur when a fracture/dislocation is reported but not confirmed by radiology review (false positives).3 While the former has the highest potential for subsequent negative clinical sequelae, overcalling pathology may also carry harm in unnecessary parental concern that their child has a fracture and the subsequent health care visits required to correct the diagnostic impression given at the initial ED visit. Overall, there is currently a paucity of data on adverse events (AEs) such as clinical and health services sequelae of a delayed correct pediatric MSK radiographic diagnosis. We determined the frequency of discrepant pediatric MSK radiographic interpretations by ED physicians relative to radiologists that led to an AE and the variables independently associated with this outcome.

**METHODS**

**Study Design and Setting**

This was a prospective cohort study conducted in an urban university-affiliated tertiary care children’s ED. The study institution is a Level I trauma center and treats approximately 80,000 children per year. This study was approved by the study institution’s research ethics board.

**Study Population**

**Patients.** We enrolled children from birth to 18 years of age who presented to the study institution’s ED between 08:00 and 23:00 hours with a chief complaint of extremity injury and received imaging. Children were excluded if they presented with imaging completed prior to the index ED visit, re-presented to the ED with an injury whose radiographs were already included in the study, presented as a Level I trauma patient, had orthopedics/plastics/radiology consultation prior to study capture of ED physician diagnostic impression, and/or had an inconclusive ED radiograph diagnosis based on radiology review. Children whose parents lacked phone or e-mail access and had an insurmountable language barrier were not eligible to participate in the study.

**ED Physicians.** All physicians who worked at the study institution’s ED during the study period were eligible for inclusion and were comprised of those certified in pediatrics, emergency medicine, and pediatric emergency medicine.

**Definitions**

A fracture was defined as a radiographically evident disruption in the bony cortex or on pediatric elbow radiographs the isolated presence of a posterior fat pad. A concordant ED physician radiograph interpretation occurred when the ED physician’s and radiologist’s diagnosis agreed on the presence or absence of fractures and/or dislocations. An ED physician radiograph discordant interpretation occurred when the ED physician and radiologist disagreed on the presence or absence of fractures and/or dislocations. An adverse event (AE) was defined as unintended harm to the patient related to the health care provided to the patient rather than the patient’s underlying medical condition.21 From a patient-oriented perspective,21 and results from a survey to pediatric orthopedic surgeons,22 an AE occurred if a ED discordant interpretation error resulted in functional/cosmetic complications or an operative intervention due to a delay in correct diagnosis and/or subsequent ED or specialty (orthopedic/plastics) visits, which served primarily to change the management prescribed at the index ED visit. We determined that a subsequent ED or specialty visits served primarily to change the
management prescribed at the index ED visit from information available at phone follow-up with the patient and/or from data recorded in the medical record. The two scenarios that met criteria for this outcome were as follows: the patient had been called back to the ED to apply the correct treatment for a fracture that was missed at the index ED visit or the patient had specialty follow-up scheduled for a radiographically visible fracture identified at the index ED visit that upon radiograph review by radiology and the specialist there was no radiograph-visible fracture; at this visit, the specialist advised the family that in fact there was no fracture and any immobilization placed in the ED was removed. This task was performed for all discrepant and a sample of nondiscrepant cases (see details below) collaboratively by two emergency physicians (KB, FA), and during this review, these physicians were blinded to the assignment of discrepant versus nondiscrepant ED radiograph interpretation.

A pediatric MSK extremity injury was considered a mild injury if supportive management (sling, splint, brace) and follow-up with the primary care physician was prescribed. An injury of moderate severity included those that required immobilization and outpatient follow-up with an orthopedic/plastic surgeon. A severe injury included those that required an urgent orthopedic intervention (e.g., fracture reduction, operation) and/or hospitalization. At the study institution, distal radius buckle fractures and nondisplaced distal fibular Salter-Harris I or II and avulsion fractures are treated with a removable splint and follow-up with the primary care physician and thus were classified as “mild injuries.” At the study institution, orthopedics/plastics is consulted for any patient that may require an emergent fracture reduction or stabilization. For those stable injuries that do not require an emergent or urgent procedure or those postprocedure that are dischargeable, it is routine practice to refer moderate to severe injuries to the orthopedic or plastics hand clinic, and patients are seen within 1 week of the index ED visit. It is not routine practice to refer mild injuries such as soft tissue or the aforementioned minor stable fractures to the orthopedic clinic.

**Patient Recruitment**

Research assistants were present from 08:30 to 23:00 daily, screened the ED electronic tracking system, and interviewed patients. In cases with confirmed eligibility, informed consent and assent where applicable was obtained from parents/guardians and patients.

**Study Interventions**

**ED.** In enrolled patients, ED attending physicians completed a data collection form that documented physician certification (pediatrics, emergency medicine, pediatric emergency medicine), and the ED physician’s number of years since graduation (0–5, 6–10, 11–15, 16–20, >20 years). We also collected patient demographic information (age, sex) and injury data: mechanism (fall < 1 m, fall ≥ 1 m, direct blow, crush, other), setting of injury (competitive sport, motor vehicle, recreation), number of injuries (one, two, three, other), body part injured, physical examination findings (deformity, swelling, tenderness, limitation of movement, neurovascular compromise, and Bieri Faces Pain Score score (0, 2, 4, 6, 8, 10)). Information on season (winter, spring, summer, fall) and time of shift (08:00–15:59, 16:00–23:59) was documented. Finally, preradiograph interpretation, physician pretest probability of a fracture/dislocation (≤10%, 11%–20%, 21%–30%, 91%–100%), and clinical impression of severity of injury (mild, moderate, severe) were documented.

Upon image review, physicians documented their opinion on the presence or absence of any fracture/dislocation and where relevant the location of the fracture/dislocation present. Physicians also documented if they interpreted the radiograph before or after they examined the patient, and the certainty of their response (very certain, certain, neither certain/nor uncertain, uncertain, very uncertain).

**Routine Radiology Review of ED Images.** As part of routine clinical operations at the study institution, ED physicians are required to document their interpretation of a radiograph on the picture archiving and communications system (PACS). All radiographs taken as part of an ED visit are then interpreted by one of the study institution’s 24 pediatric radiologists. This typically occurs within 24 hours, after patient discharge, and often review occurs the morning following the initial ED encounter. As part of routine clinical quality assurance operations at the study institution, any interpretations by the radiologist that differ from that recorded by the ED physician at the index ED visit are reported to the ED attending physician on duty the next day. Radiologists are also available 24 hours a day, 7 days a week for real-time consultation of ED images on an as needed basis.
Determination of Discordant Interpretations. All radiology diagnostic reports recorded on PACS were compared to the ED physician interpretation recorded on the clinical research form. The assignment of concordant or discordant was initially made by one ED physician (FA) in accordance with the aforementioned definitions and then all discordant cases were reviewed again to confirm this assignment in a consensus review by two ED physicians (FA, KB). Any questionable cases were further reviewed on a case-by-case bases with one study radiologist (JS) and one orthopedic surgeon (MC). Furthermore, all cases with discordant interpretations and a sample of those with concordant interpretations (every sixth concordant case to a matched number of discordant cases) were independently reviewed by one of two masked pediatric MSK radiologists (JP, JS). The case load was split evenly between radiologists for review, and the first 50 cases from each case load was interpreted by both radiologists to determine inter-rater agreement. If there were any cases where the pediatric MSK radiologists disagreed with the routine clinical radiology diagnosis, the final diagnosis of these cases was determined using consensus opinion between the two pediatric MSK radiologists (JP, JS) and the collaborating orthopedic surgeon (MC).

Patient Follow-up. All cases with discordant interpretations and a sample of those with concordant interpretations (every sixth concordant case) received phone follow-up within 3 weeks of their discharge from the index ED. This phone call served to document if there were any other health care interventions (physician follow-up, diagnostic imaging, immobilization changes) for the extremity injury(ies). Furthermore, the study institution’s medical records of these patients were reviewed to cross-reference the information provided to us by families with respect to follow-up interventions.

Outcomes

The primary outcome was the frequency of discordant ED physician radiograph interpretations that led to an AE. This was based on image review by two pediatric emergency physicians, two pediatric MSK radiologists, and an orthopedic surgeon; data gathered from the phone follow-up; and review of the patient medical record at the study institution. We also determined the variables independently associated with this outcome. An a priori list of variables that may be associated with this outcome was developed by review of the literature and content expertise provided by three pediatric emergency physicians, an orthopedic surgeon, and two pediatric MSK radiologists. Physician variables included trainee present (yes vs. no); pediatric emergency medicine credentialed attending physician (yes vs. no); and years postgraduation from all training (<10 years vs. ≥10 years). Patient variables included age (years), sex (male vs. female), fall mechanism of injury (yes vs. no), and anatomical location of injury (joint vs. other). Physician diagnostic impressions included pretest probability of a fracture/dislocation ≤ 20% (yes vs. no), clinical assessment of injury (mild vs. moderate/severe), pain score (≤2 vs. >2), review of the radiograph before patient examination (yes vs. no), and an ED physician declaration of uncertainty in diagnostic interpretation (yes vs. no). Finally, temporal factors included spring/summer season (yes vs. no) and day shift (yes vs. no).

Data Analyses

Based on prior research, we estimated that 5% of pediatric MSK discordant radiograph interpretations would lead to an AE (defined above) and considered a two-sided 95% CI with a precision of ±1%, which yielded a minimal sample size of 1,927 participants (PASS, Version 11.0.7, NCSS, LLC).

Interpretations were analyzed per radiograph set for a specific body part (e.g., wrist radiographs). Results were summarized using descriptive statistics. Means were reported with standard deviation (SD), medians with interquartile range, and proportions with respective 95% confidence intervals (CIs). Independent proportions were compared with a chi-square test. The association of variables with the outcome of ED physician radiology discordant interpretations that led to an AE was determined using logistic regression. To select the variables entered into the logistic regression model, we conducted a univariate analysis to assess if a particular variable was associated with the outcome of interest. Independent variables with a p < 0.20 were entered into a direct multivariable logistic regression model retained in the final model if p < 0.05. Variables entered into the model were also tested for collinearity and confounding effects. Goodness of fit of final model to the data were tested using the Hosmer-Lemeshow test. The odds of a discordant interpretation for a given variable were reported with respective 95% CI. All analyses were completed using SPSS for
RESULTS

Patient and Physician Demographics

Between April 1, 2016, and March 31, 2018, a total of 3,946 children with extremity injuries with imaging presented to the ED. Of these, 3,721 (94.3%) were screened for the study; 2,302 (61.9%) children met eligibility criteria and were enrolled into the study (Figure 1). The mean (±SD) age of enrolled children was 9.0 (±4.4) years, 1,288 (56.0%) were male, and 859 (37.3%) presented after a fall-type mechanism. Furthermore, 2,258 (98.1%) had a single area of injury and 977 (42.4%) children were diagnosed with a fracture/dislocation.

For the 2,302 enrolled children, 1,496 (65.0%) interpretations were performed by pediatric emergency faculty, 679 (29.5%) were interpreted by pediatricians/other pediatric subspecialties, and 127 (5.5%) were interpreted by those with general emergency medicine credentialing. Furthermore, 1,341 (58.3%) of the interpretations were done by those in practice for < 5 years, while 271 (11.8%), 264 (11.5%), 59 (2.7%), and 367 (15.9%) were performed by those in practice 6 to 10 years, 11 to 15 years, 16 to 20 years, and > 20 years, respectively.

Diagnostic Imaging Review

The pediatric MSK radiologists’ review included 490 cases, and the diagnostic agreement between the pediatric MSK radiologists demonstrated an intraclass correlation coefficient of 0.94 (95% CI = 0.90 to 0.97). The study pediatric MSK radiologists identified 35 (7.1%) minor secondary fractures not seen on routine radiology review that would not have changed the patient’s management.

Discordant ED Physician Radiograph Interpretations

Of the 2,302 injuries, 247 (10.7%, 95% CI = 9.5 to 12.1) radiographs had ED physician interpretation errors and 180 (7.8%, 95% CI = 6.8 to 9.0) had ED

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Figure 1 Patient enrollment.
physician discordant radiograph interpretations associated with an AE (primary outcome). In 123 of 180 (68.3%, 95% CI = 61.2 to 74.7), a fracture was missed entirely (n = 101) or misclassified as a more minor fracture (n = 22) at the index ED visit; 29 of 123 (23.5%) were minor, 88 (71.5%) were moderate, and six (4.9%) were severe fractures (Table 1). In 57 of 180 (31.7%, 95% CI = 25.3 to 28.8) cases, the ED physician overcalled a fracture (Table 2). The frequency of discordant radiograph interpretations varied by body region (p = 0.001) and were most frequently seen in the ankle, foot, hand, wrist, lower leg, and elbow (Figure 2).

After all significant predictors were adjusted for (Table 3), physician pretest probability of ≤ 20% versus > 20% that a fracture is present (adjusted odds ratio [aOR] = 1.6), pain score ≤ 2 vs. >2 (aOR = 1.6), injury located in a joint versus other location (aOR = 1.7) remained predictive of an ED discordant interpretation error that led to an AE (Table 3). In the resultant model, the Hosmer-Lemeshow goodness-of-fit test did not reject the null hypothesis of good fit (p = 0.4).

Patient Follow-up: Phone and Medical Record Review

Institutional medical records of all 245 discordant and 372 concordant cases were reviewed, and these cases were also telephoned within 3 weeks of the index ED

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Radiology Review Confirmed a Fracture Not Seen by the Emergency Physician and Led to an Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Fractures (n = 29)</td>
<td>Moderately Severe Fractures (n = 88)</td>
</tr>
<tr>
<td>No fracture identified by emergency physician, but fracture was present on radiology review</td>
<td></td>
</tr>
<tr>
<td>Clavicle fracture</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Proximal humerus fracture</td>
<td></td>
</tr>
<tr>
<td>Radial neck fracture</td>
<td>9 (10.2)</td>
</tr>
<tr>
<td>Supracondylar Type I fracture</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Displaced medial epicondylar fracture</td>
<td></td>
</tr>
<tr>
<td>Distal radius buckle fracture</td>
<td>10 (34.5)</td>
</tr>
<tr>
<td>Distal radius Salter-Harris II fracture</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Distal ulna minor fracture in isolation</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Distal radius/ulna bowing fracture</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Finger fracture</td>
<td>23 (26.1)</td>
</tr>
<tr>
<td>Scaphoid fracture</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Distal femur cortical buckle fracture</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Tibial spine fracture</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Patella avulsion fracture</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Toddler’s fracture</td>
<td>6 (6.8)</td>
</tr>
<tr>
<td>Distal fibula avulsion fracture</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Distal fibula Salter-Harris II fracture</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Distal tibia Salter-Harris II fracture</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Distal tibia Salter-Harris III fracture (Tillaux)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Distal tibia Salter-Harris IV fracture</td>
<td></td>
</tr>
<tr>
<td>Foot fracture</td>
<td>4 (4.5)</td>
</tr>
<tr>
<td>Toe fracture</td>
<td>6 (6.8)</td>
</tr>
<tr>
<td>Fracture identified by emergency physician but was mislabeled as a more minor fracture or the emergency physician missed a second more serious fracture</td>
<td></td>
</tr>
<tr>
<td>Monteggia—identified ulnar fracture but missed associated radial head dislocation</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Distal radius Salter-Harris II—diagnosed as distal radius buckle fractures</td>
<td>11 (12.5)</td>
</tr>
<tr>
<td>Distal radius greenstick/transverse fracture—diagnosed as distal radius buckle fracture</td>
<td>8 (9.1)</td>
</tr>
<tr>
<td>Distal tibia Salter-Harris IV—diagnosed as a distal tibia Salter-Harris II fracture</td>
<td>2 (33.4)</td>
</tr>
</tbody>
</table>

Data are reported as n (%).
visit. Overall, we achieved successful phone follow-up in 477 of 617 (77.3%) cases. Of the cases with a discordant ED radiograph interpretation, 151 of 180 (83.4%) had data captured at the phone follow-up.

Patient report and medical record review did not reveal any functional/cosmetic complications or operative procedures that resulted from a delay in diagnosis of a fracture. However, relative to cases with concordant radiograph interpretations, patients with false-negative ED radiograph interpretations encountered 77.2% more subsequent ED visits to apply immobilization and schedule appropriate follow-up for the child’s fracture, while children with false-positive radiograph interpretations experienced 41.5% additional orthopedic/plastic surgery visits to remove unnecessary immobilization placed at the index ED visit and provide anticipatory guidance for a soft tissue injury (Table 4).

DISCUSSION

This study demonstrated that approximately one in 12 pediatric MSK radiographs interpreted by pediatric ED physicians had discrepant radiograph interpretations that resulted in an AE. Specifically, discordant ED interpretation errors did not result in any cosmetic/functional issues or operative procedures due to a delay in the correct diagnosis; however, relative to patients with concordant ED radiograph interpretations, discordant interpretations did result in significantly more subsequent visits to the ED and specialty clinics to correct diagnostic impressions and provide the most appropriate management for the child’s injury. Those radiographs at highest risk of this outcome occurred when the physician reported a low pretest probability of a fracture, the patient reported a low pain score, and when the injury was located at a joint.

We demonstrated that ED physician discrepant pediatric MSK radiograph interpretations that led to an AE occurred with regular frequency across a variety of extremity injuries. Consistent with prior work,1,20 injuries located in the hand, elbow, wrist, ankle, and foot were the most common areas of discordant interpretations. However, it is reassuring that while about two-thirds of these discordant interpretations represented an undercall of a fracture, missing a serious fracture was relatively rare, and we did not identify any clinical complications that resulted from a delay in

<table>
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<th>Table 2</th>
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<tr>
<td><strong>Radiographically Evident Fracture Identified by the Emergency Physician but Radiology Review Did Not Confirm a Radiographically Evident Fracture and Led to an Adverse Event</strong></td>
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<table>
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<tr>
<th>False-positive fracture</th>
<th>n = 57</th>
</tr>
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<tbody>
<tr>
<td>Proximal humerus</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td>Supracondylar type I</td>
<td>8 (14.0)</td>
</tr>
<tr>
<td>Distal radius buckle</td>
<td>4 (7.0)</td>
</tr>
<tr>
<td>Distal ulna buckle</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Scaphoid</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td>Finger</td>
<td>13 (22.8)</td>
</tr>
<tr>
<td>Toddler</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>Distal fibula Salter-Harris II or avulsion</td>
<td>11 (19.3)</td>
</tr>
<tr>
<td>Toe</td>
<td>11 (19.3)</td>
</tr>
</tbody>
</table>

Data are reported as n (%).

Figure 2 (A) False-negative cases (undercalled pathology) associated with an AE per body region as a percentage of total number of cases with fractures (B). False-positive cases (overcalled pathology) associated with an AE per body region as a percentage of total number of cases without radiographically visible fractures. AE = adverse event.
the correct diagnosis of a serious fracture at the index ED visit. Nevertheless, the latter should be put in the context of a clinical setting that routinely includes radiology interpretation within 24 hours of the index ED visit, minimizing the possibility of complications from a delayed diagnosis of a fracture. In areas of the world with significantly delayed or absent radiology review of ED physician interpretations, the clinical consequences of a missed fracture at the index ED visit may have greater clinical relevance, and while missing a serious fracture by ED physicians only occurred in two of 1,000 of all cases, given the frequency of pediatric MSK injuries that present on a global scale, this could still lead to functional morbidity for a significant number of patients if these fractures/dislocations are not captured in a timely fashion. Regardless, in our study,
the most significant impact was the extra visits to the ED and specialty clinics, which is consistent with other studies examining the impact of medical error.32

This study focused on the perceptual errors made by ED physicians, which occur when a physician fails to identify the abnormality or overcalls an abnormality.33 Perceptual interpretation errors may be the result of diminished content expertise or the influence of cognitive biases on image interpretation.32,34 A lack of content expertise may explain, for example, why interpretation errors are more likely to occur in the joint, an area of higher radiographic complexity.2,3 The variables of low pretest probability of a fracture or a low patient-reported pain score were also found to predict pediatric MSK radiograph interpretation errors. Although this may be a reasonable mechanism of balancing sensitivity with specificity given these cases are not likely to have a fracture, this initial diagnostic impression may have influenced the ED physician to review the radiograph in a way that confirmed an a priori low clinical suspicion for a fracture, rather than scrutinizing the images more carefully for the presence of a fracture.32 Alternatively, in several cases, the ED physician identified a fracture but did not correctly identify the more serious fracture (e.g., ulna vs. Monteggia fracture). This may have been the result of search satisficing, a cognitive bias that leads to underdiagnosis in radiograph interpretation and results from decreased vigilance and/or awareness for abnormalities after identifying an abnormality.32 Interestingly, contrary to prior literature,7,9 neither degree of physician confidence nor shift time was a predictor for an ED clinically significant radiograph interpretation error. Overall, we suggest that ED physicians exercise increased vigilance and/or consider radiology consultation in cases where the injury is located in a joint and there is a low clinical suspicion of a fracture.

Our results have practice implications. The interpretation of pediatric MSK radiographs has been shown to be relatively deficient among graduating pediatric and emergency medicine residents,135–38 and therefore it is not surprising that there are interpretation errors among practicing physicians. Thus, the introduction of effective education strategies that target pediatric MSK radiograph interpretation into residency and continued professional development may be important to reduce errors among practicing ED physicians. An online evidence-based pediatric MSK radiograph interpretation system has been developed and has demonstrated effective learning outcomes to a competency standard, and this could be integrated into ED residency training.1,39 Espinosa and Nolan10 described an educational process at their site where all staff reviewed all clinically significant discrepancies at monthly meetings and created a teaching file of errors. This, alongside bringing radiographs to the emergency physician for interpretation with no radiology overread during the ED visit, significantly reduced ED physician bedside false-negative errors.10 Furthermore, to combat the influence of cognitive biases on image interpretation, especially in cases of low clinical suspicion of a fracture, physicians can use metacognitive training that encourages reflective thinking and self-questioning of a diagnosis to minimize missing or underdiagnosing fractures.32,34 Ultimately, promising artificial intelligence solutions that will aid physician imaging diagnoses may also serve to reduce these types of bedside errors.40

LIMITATIONS

This study has limitations that warrant consideration. We did not have telephone follow-up of all enrolled cases. Thus, some patients may have experienced follow-up or complications that were not captured, thereby potentially underestimating our outcomes. While we tried to optimize the reference standard by having additional radiograph reviews by a pediatric MSK radiologist of all identified discordant and a sample of nondiscordant radiographs, we did not conduct this additional review for all radiographs where both the ED physician and the radiologist agreed; thus, some of these cases may have had an incorrect final diagnosis. About 10% of patients were excluded since physicians reviewed their interpretation with a radiologist/orthopedic surgeon prior to study capture. These images may have represented more difficult cases and thus the exclusion of these cases may have resulted in an underestimate of actual ED physician interpretation error. Due to ethical restrictions at the study institution, we could not collect data on patients who declined to consent to study participation. Hence, we could not analyze their demographics or radiograph interpretations to see if these patients differed from those enrolled.

The small sample size of patients with severe fractures and the relatively short follow-up period limits this study’s ability to be certain about the clinical impact that results from ED physician discordant pediatric MSK radiograph interpretations. Due to
feasibility, this study did not include Level I trauma patients or patients who presented during overnight hours and therefore did not have the opportunity to examine if these populations are susceptible to ED physician MSK radiograph interpretation errors. Finally, this study was conducted at a single tertiary care pediatric center, and thus the results may not be generalizable to other practice settings.

CONCLUSIONS

Emergency physician discordant pediatric musculoskeletal radiograph interpretations that resulted in an adverse event occurred with regular frequency in a pediatric ED setting. AEs were primarily an increase in subsequent health care visits to correct the management prescribed at the index ED visit. A low clinical suspicion for a fracture or injury located in the joint were risk factors for ED physician discordant interpretations. Radiology consultation during the ED visit for cases at highest risk of interpretation errors, education, metacognitive training and cognitive forcing strategies, and promising artificial intelligence solutions may all serve to reduce ED physician pediatric musculoskeletal radiograph interpretation error at the bedside.

ACKNOWLEDGEMENTS

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References

Impact of Emergency Department Tele-intake on Left Without Being Seen and Throughput Metrics

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ABSTRACT

Objectives: More than 2 million patients present to a U.S. emergency department (ED) annually and leave without being seen (LWBS) due to delays in initiating care. We evaluated whether tele-intake at the time of presentation would reduce LWBS rates and ED throughput measures.

Methods: We conducted a before-and-after study at an urban community hospital. The intervention was use of a tele-intake physician to triage patients from 11 AM to 6 PM, 7 days per week. Tele-intake providers performed a triage history and physical examination, documented findings, and initiated orders in the medical record. We assessed the impact of this program using the domains of the National Quality Forum framework evaluating access, provider experience, and effectiveness of care. The main outcome was 24-hour LWBS rate. Secondary outcomes were overall door to provider and door to disposition times, left without treatment complete (LWTC), left against medical advice (AMA), left without treatment (LWOT), and physician experience. We compared the 6-month tele-intake period to the same period from the prior year (October 1 to April 1, 2017 vs. 2016). Additionally, we conducted a survey of our physicians to assess their experience with the program.

Results: Total ED volume was similar in the before and after periods (19,892 patients vs. 19,646 patients). The 24-hour LWBS rate was reduced from 2.30% (95% confidence interval [CI] = 2.0% to 2.5%) to 1.69% (95% CI = 1.51% to 1.87%; p < 0.001). Overall door to provider time decreased (median = 19 [interquartile range (IQR) = 9 to 38] minutes vs. 16.2 [IQR = 7.8 to 34.3] minutes; p < 0.001), but ED length of stay for all patients (defined as door in to door out time for all patients) minimally increased (median = 184 [IQR = 100 to 292] minutes vs. 184.3 [IQR = 104.4 to 300] minutes; p < 0.001). There was an increase in door to discharge times (median = 146 [IQR = 83 to 231] minutes vs. 148 [IQR = 88.2 to 233.6] minutes; p < 0.001) and door to admit times (median = 330 [IQR = 253 to 432] minutes vs. 357.6 [IQR = 260.3 to 514.5] minutes; p < 0.001). We saw an increase in LWTC (0.59% [95% CI = 0.49% to 0.70%] vs. 1.1% [95% CI = 0.9% to 1.2%]; p < 0.001), but no change in AMA (1.4% [95% CI = 1.2% to 1.6%] vs. 1.6% [95% CI = 1.4% to 1.78%]; p = 0.21) or LWOT (4.3% [95% CI = 4.1% to 4.6%] vs. 4.4% [95% CI = 4.1% to 4.7%]; p = 0.7). Tele-intake providers thought tele-intake added value (12/15, 80%) and allowed them to effectively address medical problems (10/15, 67%) but only (10/15, 67%) thought that it was as good as in-person triage. Of the receiving physicians, most agreed with statements that tele-intake did not interfere with care (19/22, 86%), helped complement care (19/21, 90%), and gave the patient a better experience (19/22, 90%).

Conclusions: Remote tele-intake provided in an urban community hospital ED reduced LWBS and time to provider but increased LWTC rates and had no impact on LWOT.
Background

From 2006 to 2014, emergency department (ED) visits increased by 14.8% with 140 million visits in 2014. Despite this increase, the overall number of EDs decreased during this time. Although ED crowding is recognized as a public health crisis, it persists. ED crowding is associated with longer wait times to be seen, increasing number of patients who leave without being seen (LWBS), poorer access, worse patient experience, decreased quality of care, and adverse consequences on health system finances. Several strategies have been proposed to decrease LWBS rates and improve ED throughput. These include standing order placement by triage nurses, augmenting the standard triage process by placing a physician or advanced practice provider in triage, and expansion of observation units to decrease the number of boarders. All of these either require increased on-site staffing or are not that effective in impacting overall patient flow or LWBS rates.

Telehealth, using remote synchronous audio-video communication between patients and providers, has been shown to increase access, decrease costs, improve patient experience and be effective across a variety of clinical indications. We are unaware of any published studies evaluating the impact of tele-intake on the LWBS rate and ED throughput measures for all patients presenting to the ED.

The National Quality Forum (NQF), a nonpartisan organization dedicated to catalyzing improvements in healthcare, recognized the need to create a framework for measures to evaluate telehealth. The goal of our study was to evaluate the impact of an ED tele-intake program on access, provider experience and effectiveness of care, which are three of the four domains of the NQF telehealth measures framework.

Study Setting and Population

The study was conducted at Methodist Hospital, a community hospital affiliated with Jefferson Health that has an annual ED census of approximately 40,000 visits. Attending physician coverage is available for 40 hours per day on weekdays and 39 hours per day on weekends. There is an advanced practice provider 24 hours daily. The hospital leadership had attempted various measures to improve their metrics of LWBS and time to provider over the 2 years prior, including nursing order sets, immediate bedding, physician incentives, and physician engagement, with no significant change in these metrics.

Jefferson Health launched a telehealth program (Jeff Connect) that provides patients with on-demand care via synchronous audio-video link with a Jefferson-employed emergency medicine physician 24 hours per day, 7 days per week. Tele-intake responsibilities were added to the on-demand physician without requiring any incremental staffing. This provider was not on site but credentialed at the hospital. During the study period, tele-intake was performed for 7 hours per day (11 AM to 6 PM), 7 days per week. Tele-intake responsibilities were also covering on-demand, direct-to-consumer, synchronous audio-video visits as the only other clinical responsibility during this 7-hour period. We found that the physician was able to see 94% of tele-intake patients during the 7-hour period. These hours were chosen based upon ED visit volumes and ability to integrate tele-intake into this already existing coverage during this time frame.

All patients who presented to the ED during the hours of 11 AM to 6 PM daily were eligible for inclusion (i.e., tele-intake). Emergency medical services patients who were stable enough to go through triage were also included. The only exclusion was the requirement for an interpreter.

Methods

Study Design

This was a before-and-after study evaluating the impact of an ED tele-intake program on LWBS rate and ED flow metrics in an urban community ED that had a traditional nurse triage model prior to implementation. We compared the 6-month tele-intake period to the same period from the prior year (October 1 to April 1, 2017 vs. 2016). The study protocol was reviewed and approved by the institutional review board at Thomas Jefferson University.

Study Protocol

Patients entered the ED through the same processes as prior to implementation of tele-intake. After obtaining vital signs and a chief complaint, either the triage nurse or the nurse in the room (if the patient was directly bedded) would activate the tele-intake platform (EMOpti, Inc., Brookfield, WI). The platform was installed on a stationary computer in the triage room, as well as two mobile computers that could be rolled into patient rooms. The tele-intake physician would be logged in from 11 AM to 6 PM and viewed a command
console that placed all pending patients into a queue. Once the encounter was accepted, a synchronous “real time” audio-video connection was established. A mobile webcam facilitated the physical examination. The physician documented a brief note and placed the appropriate orders to initiate care. Patients were considered seen by a provider after tele-intake physician evaluation. Care was then transferred to the on-site provider in the ED. The on-site provider would look at tele-intake notes for clarification; direct communication between two providers was rare as triage registered nurse would communicate any concerns directly. Patients were not discharged directly from tele-intake. Disposition times were based on the time discharged patients left the ED or the time stamp on the admission order.

**Measures**

Data collected include patient demographics (age, gender), hour of arrival, patient dispositions, and ED flow metrics (door to provider, door to discharge for all patients, decision to admit, ED length of stay for discharged patients, and ED length of stay for patients admitted or placed in observation). LWBS was defined as not seeing either a tele-intake or on-site provider. Patients who saw a tele-intake physician and left prior to seeing onsite provider were defined as left without treatment complete (LWTC). Patients who left after tele-intake and had been seen by an in-person provider but prior to completion of the evaluation and disposition were defined as left against medical advice (AMA). Left without treatment (LWOT) was defined as the composite of all patients who LWBS, LWTC, or AMA.

**Outcomes**

Outcomes for assessment were determined using the NQF framework for telehealth measurement, which includes experience, access, and effectiveness. Our primary outcome was effectiveness, measured by 24-hour LWBS rate. Secondary outcomes were door to provider, ED length of stay for discharge, ED length of stay for patients admitted or placed in observation, LWTC rate, AMA rate, and LWOT rate for the 24-hour time period as well as for the 7 hour of tele-intake coverage. In addition, we assessed provider experience.

**Provider Experience**

To assess provider experience, we surveyed providers that performed tele-intake as well as those providers who worked in the ED (on the receiving end of patients who were tele-intaken). Tele-intake providers received three questions using a 6-item Likert scale (without neutral to force answers): 1) tele-intake allows me to add value to my patient’s ED experience; 2) tele-intake allows me to effectively address and impact the patient’s medical outcomes; and 3) compared to in-person triage, tele-intake gives me the same ability to appropriately evaluate and initiate care for patients. Providers then had free-text questions about the ways to further improve workflow and care.

The receiving ED physicians who received patients after tele-intake had three questions with the 6-item Likert scale: 1) tele-intake gives my patient a better ED experience, 2) tele-intake does not get in the way of my ability to care for my patient, and 3) tele-intake helps complement my care for patients in the ED. There were two similar free-text questions about ways to improve workflow and care. Answers were grouped as follows: strongly agree, agree, and slightly agree were considered positive responses and disagree, slightly disagree, and strongly disagree were considered negative responses.

**Data Analysis**

Baseline characteristics of the patients were recorded. Data are described as means with standard deviations or medians with interquartile ranges. We assessed the median time to provider before and after the intervention. We used t-testing for continuous variables, chi-square analysis for proportions, and Wilcoxon rank-sum testing for nonparametric variables. Data were abstracted from the medical record (EPIC) using Qlik. Analyses were performed for the overall day (24 hours/day) and isolating the 7-hour period of tele-intake. Data analyses were performed using Stata v14 (StataCorp). Due to the large fixed size of the cohort, no formal sample size was performed.

**RESULTS**

During the 6-month before-and-after study periods, overall ED volumes were similar (19,892 vs. 19,646) based on hour of arrival (Figure 1). Patients were similar with respect to gender (53.9% vs. 53.3% female, p = 0.28) but during the tele-intake period, patients were older (46.2 ± 21.2 years vs. 46.7 ± 21.3 years, p = 0.002).

Comparing the before and after study periods, the 24-hour LWBS rate was reduced (2.30% [95%
CI = 2.09% to 2.51% to 1.69% [1.51% to 1.87%]; p < 0.001). Throughput times of door to provider and door to decision to admit decreased. However, overall length of stay, door to discharge times, and door to admit times increased (Table 1). There was no overall change in the number of patients who LWOT, because there was an increase in the number of patients who LWTC (Table 1).

Analyzing presentations during the hours of tele-intake only (11 AM to 6 PM), the before and after periods were similar with respect to volumes (9,372 vs. 9,261) as well as patient age and gender. The 7-hour LWBS rates were reduced (2.58% [95% CI = 2.27% to 2.90%] to 1.84% [95% CI = 1.57% to 2.11%]; p < 0.001). While 7-hour LWTC increased (0.66% [95% CI = 0.5% to 0.8%] to 1.7% [95% CI = 1.4% to 2.0%]; p < 0.001) the LWOT remained the same (4.2% [95% CI = 3.8% to 4.6%] vs. 3.9% [95% CI = 3.6% to 4.3%]; p = 0.11). There was a decrease in door to provider time (median = 23 [IQR = 11 to 48] minutes vs. 14.5 [IQR = 7.1 to 30.5] minutes; p < 0.001). Door to decision to admit improved; however, ED length of stay, door to discharge, and door to admit times increased (Table 1).

**Provider Experience**
A total of 15 of 17 tele-intake providers (88%) responded to the survey. Fourteen responded positively that “tele-intake allows me to add value to my patient’s ED experience,” 12 that “tele-intake allows me to effectively address and impact the patient’s medical outcomes,” and 10 that “compared to in-person intake, tele-intake gives me the same ability to appropriately evaluate and initiate care for patients.” Three responded negatively to “tele-intake allows me to effectively address and impact the patient’s medical outcomes” and two that “compared to in-person intake, tele-intake gives me the same ability to appropriately evaluate and initiate care for patients.”

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient Demographics and Outcomes Before and After Tele-intake Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before (Oct 1, 2016-Apr 1, 2017)</td>
</tr>
<tr>
<td>All patients (24 hours daily)</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>19,892</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>46.2 ± 21.2</td>
</tr>
<tr>
<td>% Female</td>
<td>53.9</td>
</tr>
<tr>
<td>LWBS rate (%)</td>
<td>2.3 (2.09–2.51)</td>
</tr>
<tr>
<td>LWTC rate (%)</td>
<td>0.59 (0.49–0.70)</td>
</tr>
<tr>
<td>AMA rate (%)</td>
<td>1.4 (1.2–1.6)</td>
</tr>
<tr>
<td>LWOT rate (%)</td>
<td>4.3 (4.1–4.6)</td>
</tr>
<tr>
<td>ED length of stay (minutes)</td>
<td>184 [100–292]</td>
</tr>
<tr>
<td>Door to provider time (minutes)</td>
<td>19 [9–38]</td>
</tr>
<tr>
<td>Door to discharge time (minutes)</td>
<td>146 [83–231]</td>
</tr>
<tr>
<td>Door to decision to admit time (minutes)</td>
<td>201 [147–280.5]</td>
</tr>
<tr>
<td>Door to admit time (minutes)</td>
<td>330 [253–432]</td>
</tr>
<tr>
<td>Patients 11 AM to 6 PM</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>9372</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.0 ± 21.1</td>
</tr>
<tr>
<td>% Female</td>
<td>53.9</td>
</tr>
<tr>
<td>LWBS rate (%)</td>
<td>2.58 (2.27–2.90)</td>
</tr>
<tr>
<td>LWTC rate (%)</td>
<td>0.66 (0.5–0.8)</td>
</tr>
<tr>
<td>AMA rate (%)</td>
<td>1.2 (1–1.4)</td>
</tr>
<tr>
<td>LWOT rate (%)</td>
<td>4.2 (3.8–4.6)</td>
</tr>
<tr>
<td>ED length of stay (minutes)</td>
<td>183 [93–297]</td>
</tr>
<tr>
<td>Door to provider time (minutes)</td>
<td>23 [11–48]</td>
</tr>
<tr>
<td>Door to discharge time (minutes)</td>
<td>142 [76–230]</td>
</tr>
<tr>
<td>Door to decision to admit time (minutes)</td>
<td>213 [156–289]</td>
</tr>
<tr>
<td>Door to admit time (minutes)</td>
<td>343 [265–428]</td>
</tr>
</tbody>
</table>

Data are reported as % (95% CI) or median [IQR], unless otherwise specified.
AMA = left against medical advice; LWBS = left without being seen; LWOT = left without treatment (includes LWBS, AMA and LWTC); LWTC = left without treatment complete.
evaluate and initiate care for patients” (Figure 2). For the receiving on-site physicians (response rate 22/35), 19 of 22 agreed that tele-intake gave their patients a better experience, 19 of 22 agreed that tele-intake did not get in the way of their ability to care for their patient, and 19 of 21 (one no response) agreed that it helped complement their care (Figure 3).

**DISCUSSION**

We found that having a virtual provider doing tele-intake reduced the 24-hour and 7-hour LWBS rate and improved door to provider times, as well as impacted some measures of ED throughput, but only during the 7-hour time period when it was being used. Additionally, it had an overall impact on 24-hour LWBS, even though overall door to disposition times were not improved. Associated with the decreased LWBS, we observed a corresponding increase in the LWTC group both overall and during the 7 hours of tele-intake. There was no change in overall LWOT in either
group. Although our study did not focus on this group of patients, it is not clear whether LWBS and LWTC groups represent the same or different cohorts or how receiving early radiography and testing might have factored into a LWTC decision. The lack of change of LWOT suggests that tele-intake improves ED input but not necessarily overall number of patients who stay until final ED disposition.

We believe that the lack of changes in measures of ED throughput were due to factors outside of using tele-intake. Overall ED crowding is affected by other barriers such as ED patient boarding, inpatient bed utilization, test utilization, consults, and staffing. As we did not increase our on-site ED staffing to carry out orders by tele-intake providers, some of the potential to improve overall output may not have been realized.

We assessed physician experience for both the receiving physician and the tele-intake physician, shortly after implementation. With respect to the experience of the receiving physician, 19 of 21 responded that tele-intake complimented their care, and 19 of 22 thought that it provided a better experience. Three of 22 providers thought it interfered with their ability to provide care.

With respect to the tele-intake physicians, 14 of 15 agreed it tele-intake adds value, 12 of 15 thought tele-intake allowed them to effectively address care, but only 10 of 15 thought that it was as effective as in-person physician in triage. While we did not focus on the reasons for these initial views in this paper, further work on current attitudes would be useful to gauge whether physician attitudes have changed over time.

We demonstrated effectiveness in improving ED input, as assessed by reduced LWBS and improved time to provider. In another hospital in our health system, we use a provider physically present in triage to perform the same intake process. The impact on LWBS rates using tele-intake were similar to results we found by placing a provider in triage.53 Based on our experience with a provider in triage, we believe the tele-intake process can be further improved by the addition of a nurse or tech in the intake or waiting room to expedite phlebotomy and medication administration. We hypothesize that if we provided earlier testing, in addition to earlier provider contact, patients may feel more inclined to stay to get results and feel more invested in their ED outcome helping mitigate LWTC and, in turn, improve LWOT.

There are multiple potential advantages to using tele-intake over a provider in intake. Use of a single off-site virtual provider to perform intake on patients at multiple hospitals can reduce cost of care while enhancing revenue from retaining more patients in the ED (reduced LWBS). In addition, this model could be applied to improve patient care and facilitate surge in single-coverage EDs or bring more expertise into rural areas to assist with earlier identification of patients requiring transfer. The disadvantages may include need for increased staffing, increased technology requirements (and associated licensing expenses), and standardized provider training, recognizing that tele-intake only improved our ED input (LWBS and time to provider) without improving overall throughput or LWOT.

Based on our experience during this study, we have removed a provider in triage from a second hospital and integrated those patients into our tele-intake process. Thus, we have a single-coverage provider model that is now evaluating all patients presenting to two EDs with a combined census of 100,000. Optimizing front-end resources (nursing, technicians, phlebotomy, radiology) may further expedite the evaluation. Additionally, expanding hours of operation is expected to further improve these operational efficiencies. Although our system might be unique in that we were able to add this workflow to preexisting telehealth providers and we already had a physician in intake model, increased capture of patients (and associated revenue) via reduced LWBS may help fund or at least defray the costs of this type of program in institutions that do not have these preexisting resources.

LIMITATIONS

Our study has limitations. Tele-intake was only in operation during the 11 AM to 6 PM time frame. While this biases our results toward the null and would be expected to decrease the magnitude of any benefit, we still found a benefit in LWBS reduction. Our processes will be costlier to replicate in a system that does not have preestablished or dedicated telehealth providers. Our program already had the resources, technology, and trained providers when we set up our tele-intake program, so we did not have incremental staffing costs for this program. As telemedicine is rapidly being adopted within health systems,54 those looking to implement similar programs should consider potential synergies with staffing in observation units, urgent care centers, or other telemedicine use cases to mitigate costs of a tele-intake program. Programs that already have an intake physician can convert that
position to tele-intake and cover more than one institution to achieve synergies. As a before-and-after study, there may have been secular trends that led to the decrease in LWBS that we did not account for. We did not formally assess patient experience and our provider experience surveys reflect responses after the first month of the pilot and the experiences may have changed as the program has grown. While we had a very high response rate from tele-intake physicians, our response of only 63% of on-site physicians warrants further evaluation.

CONCLUSIONS

In conclusion, the major impact of tele-intake appears to be on ED input (reduced left without being seen) rather than on total ED care as left without treatment remained the same. Further work should focus on maintaining improved metrics, effect on costs, evaluating the quality of tele-intake visits, evaluating whether advanced practice practitioners can achieve the same results, and evaluating patient experience.

References


Propofol for Treatment of Acute Migraine in the Emergency Department: A Systematic Review

Corissa Piatka, PharmD1 and Robert D. Beckett, PharmD2

ABSTRACT

Objectives: Propofol has not been extensively studied as an acute migraine therapy; however, based on the limited evidence from outpatient and inpatient settings, propofol has been proposed as an option for patients who present to the emergency department (ED). The purpose of this review was to evaluate the existing literature regarding the safety and efficacy of propofol for acute migraine treatment in the ED.

Methods: A systematic review of clinical studies of propofol treatment for acute migraine in the ED was performed using Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. Trials were identified through PubMed, Google Scholar, clinical trial registries, research registries, and key journals through May 2019. A modified Jadad scoring system was used to assess the methodologic quality of the included randomized controlled trials, and the Newcastle-Ottawa Scale was used for the retrospective cohort study.

Results: Nine studies, including five case reports or series, one retrospective cohort study, and three randomized controlled trials, consisting of 290 patients, were reviewed. All studies in adults reported propofol to be an effective therapy for migraine, but the strength of these results was limited by dosing variations, small sample sizes, and limited generalizability. Pediatric studies produced mixed results.

Conclusions: Propofol may be an effective rescue therapy for patients presenting to the ED for acute migraine, but its place in therapy based on the limited available evidence is unknown. The safety of propofol for migraine management in the ED has not been adequately examined.

Migraine headaches are a common, disabling medical condition. Within the United States, it is estimated that acute migraine attacks account for approximately 1.2 million visits to the emergency department (ED) every year.1 Treatment for migraine in the ED can include a variety of medications, including serotonin receptor agonists, corticosteroids, opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and antiemetic medications.2 The number of options, however, may become limited based on patient-specific factors, such as contraindications and previously failed outpatient regimens. These medications can also have significant adverse effects, such as akathisia or dystonic reactions with antidopaminergic therapies. Additional treatment options that work quickly to abort acute migraine and prevent migraine recurrence are still needed.2,3

Propofol is a rapid-acting intravenous (IV) anesthetic agent.4 It is most commonly used for induction or maintenance of general anesthesia or as a sedation
agent for critically ill patients. Its off-label uses include postoperative nausea and vomiting and refractory status epilepticus. Propofol is a gamma-aminobutyric acid receptor agonist, which results in its sedative and anti-convulsant effects. Its antimigraine mechanism, however, remains poorly understood. Propofol inhibits calcium influx via calcium channels, potentially preventing catecholamine-induced vasoconstriction, and may also inhibit N-methyl-D-aspartate (NMDA) receptors. NMDA receptor antagonism is believed to prevent cortical spreading depression, a neurologic process that is a possible cause of migraine and migraine aura. It has yet to be determined if propofol directly affects cortical spreading depression in human subjects.5,7

Recent evidence has suggested that propofol may be effective for treating refractory migraine and chronic headache in the outpatient and inpatient settings.3-15 In an open-label trial, Krusz et al.8 studied the use of propofol for the treatment of intractable or refractory migraine attacks in 77 patients of an outpatient headache clinic. Of these patients, 63 (82%) reported total abolition of migraine after being treated with subanesthetic propofol therapy. Drummond-Lewis and Scher14 reported a case series of two hospitalized patients who were treated with propofol for status migrainosus. In both cases, patients reported improvement in their migraine pain and the authors concluded that propofol therapy contributed to a “rapid discharge.” The success described in these cases created increasing interest in propofol as a potential agent for acute migraine. As many patients report to the ED for acute migraine attacks, we chose to focus on this setting. The purpose of this review was to evaluate the existing clinical evidence for propofol use versus other standard therapies for patients treated for acute migraine in terms of pain resolution and adverse events in the ED.

MATERIALS AND METHODS

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.16 The following databases were used: PubMed (1970 to May 2019) and Google Scholar (2000 to May 2019). To identify unpublished trials, clinical trials and research registries were searched. These included the International Standard Randomised Controlled Trials Number (ISRCTN) Register, ClinicalTrials.gov, European Union Clinical Trials Register, World Health Organization International Clinical Trials Registry Platform, National Research Registry Archive, Health Services Research Projects in Progress, and National Institutes of Health Reporter. Key journals, including Academic Emergency Medicine, Annals of Emergency Medicine, Emergency Medicine Journal, The Journal of Emergency Medicine, Headache: The Journal of Head and Face Pain, and The Journal of Headache and Pain, were hand searched from 2000 to May 2019. References of all included trials were reviewed for additional trials. The original search was completed by the first author and verified by the second author in May 2019. Search terms are summarized in Table 1. There were no language restrictions.

All identified clinical studies of adult or pediatric patients who received propofol for acute migraine treatment within the ED were included. Studies of propofol use for sedation, postoperative nausea and vomiting, status epilepticus, or general anesthesia were excluded. Literature involving nonhumans was excluded. Inclusion and exclusion criteria were applied by the first author, and the second author verified results. Differences in recommendations or inclusion or exclusion of articles were resolved by consensus.

A single reviewer extracted the following data using a standard data extraction form: trial design, setting, country, number of patients, intervention, measure of effectiveness of migraine relief, adverse effects, and results. The primary outcome evaluated effectiveness of migraine relief. Secondary outcomes included adverse effects. There were no instances of missing information for these data extraction points. Results were synthesized using change in pain rating from baseline and frequency of adverse events.

A modified, five-point Jadad scoring system (i.e., two points for randomization, two points for blinding, one point for description of withdrawals) was used to

<table>
<thead>
<tr>
<th>Terms</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol (non-MeSH) headache (non-MeSH)</td>
<td>103</td>
</tr>
<tr>
<td>Propofol (MeSH) AND headache disorders (MeSH)</td>
<td>18</td>
</tr>
<tr>
<td>Propofol (MeSH) AND headache disorders, primary (MeSH)</td>
<td>13</td>
</tr>
<tr>
<td>Propofol (MeSH) AND migraine disorders (MeSH)</td>
<td>12</td>
</tr>
<tr>
<td>Propofol (non-MeSH) migraine (non-MeSH)</td>
<td>29</td>
</tr>
</tbody>
</table>

MeSH = medical subject heading. *Nonexclusive.
assess the methodologic quality of included randomized controlled trials. The Newcastle-Ottawa Scale was used to assess quality of the single included cohort study. Scoring was completed by both authors, who resolved any differences in scoring by consensus. Given the small number of studies and anticipated between-study heterogeneity in a number of factors (i.e., study design, propofol regimen, comparator, patient populations), it was decided not to pool results in a meta-analysis. This review has not been registered and no funding was sought.

RESULTS

Nine studies were included for a total of 290 patients (Figure 1). These studies are summarized in Table 2 and consisted of five case reports or series (n = 5), one retrospective cohort study (n = 1), and three randomized controlled trials (n = 3). Two of the randomized, controlled trials were scored at a 4 and the third at a 3 using the Jadad scoring system (Table 3). The retrospective cohort study earned four of four possible stars for selection, two of two stars for comparability, and two of three stars for outcome on the Newcastle-Ottawa Scale for cohort studies, suggesting high quality.

Adults

Two case reports describing propofol therapy for migraine in the ED have been published, describing successful (though noncontrolled) treatment of migraine pain and symptoms with 30 to 60 mg of propofol administered as an IV bolus. One patient experienced mild recall deficits (although they were also confused at presentation) and narrowed visual field that resolved over time. Soleimanpour

Figure 1 Study flow (PRISMA) diagram.
<table>
<thead>
<tr>
<th>Study; study design; setting (country)</th>
<th>Intervention</th>
<th>Control</th>
<th>Cointerventions and monitoring</th>
<th>Measure of effectiveness of migraine relief</th>
<th>Baseline characteristics</th>
<th>Efficacy results</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult studies (&lt;18 years old)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mohseni and Fatehi, 2012;¹⁹ case report; ED (Iran)</td>
<td>IV propofol 60 mg once ($n = 1$)</td>
<td>N/A</td>
<td>No cointerventions; had already received dexamethasone, meperidine, metoclopramide, and promethazine; monitoring not described.</td>
<td>Descriptive report from patient—not scored or ranked</td>
<td>29-year-old female with acute migraine</td>
<td>Complete resolution of pain/symptoms; no recurrent migraine report at 72-hour follow-up.</td>
<td>Patient fell asleep for 6 hours, but no other issues reported.</td>
</tr>
<tr>
<td>Sato et al., 2017;²⁰ case report; ED (Japan)</td>
<td>IV propofol 30 to 40 mg once ($n = 1$)</td>
<td>N/A</td>
<td>Cointerventions not described; patient received a brain CT scan, brain MRI, and cerebrospinal fluid analysis and “routine blood tests.”</td>
<td>Clinician report of confusional state</td>
<td>24-year-old male with acute confusional migraine</td>
<td>Patient’s consciousness “markedly recovered,” but he could not remember confusional episode.</td>
<td>Mild difficulty in word recall, narrowed visual field.</td>
</tr>
<tr>
<td>Ward et al., 2013;²³ case series; ED (Australia)</td>
<td>IV propofol 20 mg every 10 minutes ($n = 15$)</td>
<td>N/A</td>
<td>Failed medications, cointerventions, and monitoring parameters not described.</td>
<td>VAS (0 to 10 points)</td>
<td>Median age 42 years; 80% females; baseline median pain score 8/10 (range 4–10)</td>
<td>Four of 22 cases experienced pain at treatment completion; one recurrence within 24 hours.</td>
<td>None reported.</td>
</tr>
<tr>
<td>Mosier et al., 2013;²² case series; ED (United States)</td>
<td>IV propofol 1 mg/kg ($n = 4$)</td>
<td>N/A</td>
<td>No standard cointerventions or failed medications; failed medications included sumatriptan, prochlorperazine, naproxen, and gabapentin; cointerventions included prochlorperazine, diphenhydramine, and ketorolac; monitoring parameters included vital signs.</td>
<td>Pain scale (0–10 points)</td>
<td>Age 51–62 years; baseline median pain score 9/10 (range 8–9)</td>
<td>Three of the four patients achieved complete resolution of symptoms; one patient was discharged with a pain score of 1/10; no recurrence reported.</td>
<td>One patient was discharged with a heart rate of 48; no other bradycardia, hypotension, or adverse events were reported.</td>
</tr>
<tr>
<td>Study; study design; setting (country)</td>
<td>Intervention</td>
<td>Control</td>
<td>Cointerventions and monitoring</td>
<td>Measure of effectiveness of migraine relief</td>
<td>Baseline characteristics</td>
<td>Efficacy results</td>
<td>Adverse events</td>
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<tr>
<td>Soleimanpour et al., 2012;21 case series; ED (Iran)</td>
<td>IV propofol 10 mg bolus every 5 minutes ($n = 8$)</td>
<td>N/A</td>
<td>Nonresponsive to dexamethasone, NSAIDs, opioids, and serotonin agonists; no cointerventions; monitoring not described.</td>
<td>VAS (0–10 points)</td>
<td>Age 22–44 years; six female patients; mean ± SD pain score at presentation $8.9 \pm 0.8$ (95% CI = 8.2 to 9.6); accompanying symptoms (photophobia, nausea, vomiting, phonophobia) completely resolved in all patients; two cases of recurrence in 72 hours.</td>
<td>Mean pain scores at 30 minutes after treatment initiation: $1.1 \pm 0.8$ (95% CI = 0.4-1.8); Temporary drowsiness in one patient; oxygen saturation of 98% in a second patient.</td>
<td></td>
</tr>
<tr>
<td>Soleimanpour et al. 2012;24 RCT; ED (Iran)</td>
<td>IV propofol 10 mg bolus every 5 minutes ($n = 45$)</td>
<td>Dexamethasone 0.15 mg/kg IV bolus ($n = 45$)</td>
<td>No cointerventions; monitoring included cardiac monitoring, blood pressure, capnography, pulse oximetry, and vital signs.</td>
<td>Graded page scale (0–10 points)</td>
<td>Mean age $35.7 \pm 12.6$ years vs. $36.3 \pm 13.4$ years; 66.6% vs. 62.2% female; baseline mean ± SD pain score = $8.0 \pm 1.5$ vs. $8.1 \pm 1.3$.</td>
<td>Mean ± SD pain score at 45 minutes = $1.2 \pm 1.6$ vs. $2.9 \pm 1.8$ (p &lt; 0.001); No significant difference between groups regarding mean oxygen saturation, heart rate, or blood pressure; two cases of mild oxygen desaturation ($O_2 = 89%$) with propofol, which were corrected with the use of nasal oxygen; one case of slurred speech and 20 cases of mild sedation reported.</td>
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<tr>
<td>Moshtaghion et al., 2015;25 RCT; ED (Iran)</td>
<td>IV propofol 30- to 40-mg bolus followed by 10- to 20-mg bolus every 3–5 minutes ($n = 45$)</td>
<td>Sumatriptan 6 mg subcutaneously once with option for repeated dose ($n = 45$)</td>
<td>Dexamethasone, indomethacin, or granisetron was used as rescue therapy for nonresponders; monitoring included vital signs and symptoms of ongoing migraine or adverse effects.</td>
<td>11-point VAS</td>
<td>Mean ± SD age $33.1 \pm 8.1$ years vs. $33.4 \pm 7.9$ years; 73.9% vs. 77.3% female; $93.5%$ vs. $93.2%$ chronic migraine; $93.3%$ vs. $88.9%$ failed preventative therapy; baseline pain intensity scores = $9.1 \pm 1.0$ vs. $8.7 \pm 1.2$.</td>
<td>Pain intensity scores at 30 minutes = $2.6 \pm 2.1$ vs. $3.7 \pm 2.6$, p = 0.034; Pain intensity scores at 1 hour = $2.7 \pm 2.6$ vs. $2.4 \pm 2.3$, p = 0.53; Pain intensity scores at 2 hours = $1.6 \pm 2.0$ vs. $1.4 \pm 2.0$, p = 0.53; recurrence at 24 hours = $17.1%$ vs. $55.3%$, p = 0.001; Chest tightness (2.2% vs 31.1%, p = 0.001); no hemodynamic instability or oxygen desaturation of less than 90% reported.</td>
<td>(Continued)</td>
</tr>
<tr>
<td>Study; study design; setting (country)</td>
<td>Intervention</td>
<td>Control</td>
<td>Cointerventions and monitoring</td>
<td>Measure of effectiveness of migraine relief</td>
<td>Baseline characteristics</td>
<td>Efficacy results</td>
<td>Adverse events</td>
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<td><strong>Pediatric Studies (7–19 years of age)</strong></td>
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<tr>
<td>Sheridan et al., 2012; 26 retrospective chart review; ED (United States)</td>
<td>No standardized dosing based on study design: IV propofol 10- to 50-mg bolus, could be repeated (n = 7)</td>
<td>No standardized control; patients could have received diphenhydramine, NSAIDs, and prochlorperazine (n = 7)</td>
<td>No cointerventions described; monitoring included continuous pulse oximetry and vital signs.</td>
<td>11-point VAS</td>
<td>Age 12.3 ± 3.1 years vs. 14.7 ± 2.1 years; 5/7 female in each group; 27 patients on migraine prophylaxis in each group; baseline VAS 9.5 vs. 7</td>
<td>Mean VAS reduction = 80% vs. 61% with, p = 0.02; mean length of stay 122 minutes vs. 203 minutes (p = 0.2); one patient in each group returned to the ED within 24 hours.</td>
<td>None reported.</td>
</tr>
<tr>
<td>Sheridan et al., 2018; 27 RCT; ED (United States)</td>
<td>IV propofol 0.25 mg/kg bolus (maximum bolus of 30 mg every 5 minutes for a maximum of 5 doses (n = 30)</td>
<td>Ketorolac 0.5 mg/kg IV, diphenhydramine 1 mg/kg IV, and metoclopramide 0.1 mg/kg or prochlorperazine 0.1 mg/kg (n = 36)</td>
<td>20 mL/kg normal saline administered 30 minutes prior to study drugs; monitoring included continuous cardiorespiratory, monitoring, pulse oximetry, and blood pressure.</td>
<td>11-point VAS</td>
<td>Age 14.6 ± 2.1 vs. 14.6 ± 3.0 years; 70% vs. 78% female; baseline VAS 7.9 ± 1.1 vs. 8.3 ± 1.4</td>
<td>Percent VAS reduction 51% vs. 59%, p = 0.34; absolute VAS reduction 4.0 vs. 4.8, p = 0.24; VAS 4 or less: 73% vs. 72%, p = 0.92; rebound headache: 25% vs. 67%, p = 0.01</td>
<td>One patient experienced transient oxygen desaturation to 89% that self-resolved.</td>
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</tbody>
</table>

CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; VAS = visual analog scale.
<table>
<thead>
<tr>
<th>Study</th>
<th>Was the study described as randomized?</th>
<th>Was randomization appropriate?</th>
<th>Was the study described as double blind?</th>
<th>Were randomization and blinding appropriate?</th>
<th>Was there a description of withdrawals?</th>
<th>Total Score</th>
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<tbody>
<tr>
<td>Soleimanpour et al., 2012\textsuperscript{24}</td>
<td>1</td>
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<td>1</td>
<td>4</td>
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<td></td>
<td>The study was described as randomized.</td>
<td>Patients were randomized by picking a ballot.</td>
<td>The study was described as double blind.</td>
<td>Specialists who were blinded to all study procedures performed the injections and filled out questionnaires. Curtains separating the hands and upper body of the patient from the lower body were used to blind the study personnel to the type of injection.</td>
<td>All patients were included in the analysis. No patients were lost to follow up or had to discontinue the intervention. This was stated directly in the Consort diagram.</td>
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<tr>
<td>Moshtaghion et al., 2015\textsuperscript{25}</td>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>The study was described as randomized.</td>
<td>Patients were randomized using a random number table.</td>
<td>The study was described as double blind.</td>
<td>Wrapped syringes were used to blind patients. It is stated that evaluating physicians were also blinded to the therapy, but this is not described in detail.</td>
<td>One patient had the intervention discontinued due to severe chest tightness. This was stated directly in the Consort diagram.</td>
<td></td>
</tr>
<tr>
<td>Sheridan et al., 2018\textsuperscript{27}</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>The study was described as randomized.</td>
<td>Patients were prerandomized by opaque folders prior to the study start date. These were divided evenly between two study sites. The folders were utilized sequentially during enrollment.</td>
<td>The study was not described as double blind.</td>
<td>Patients and study personnel were not blinded to the intervention.</td>
<td>Data were provided for each enrolled patient.</td>
<td></td>
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</tbody>
</table>

*Scores = 0–5 points; poor quality if \( \leq 2 \).*
et al.\textsuperscript{21} published a case series describing eight patients who received propofol in the ED for refractory migraine. All patients (mean age = 30.5 years) had migraines that lasted more than 72 hours in duration and were not responsive to other therapies, including serotonin receptor agonists, dexamethasone, opioids, or NSAIDs. Pain improvement was noted, on average, and accompanying symptoms, such as photophobia and phonophobia, were resolved in all patients. Reported adverse events included temporary drowsiness in one patient and an oxygen saturation of 89\% in a second patient. At 72 hours after ED discharge, two cases reported recurrent headache by telephone follow-up. Both were treated effectively with NSAIDs without utilization of inpatient medical treatment. In another case series published by Moshtaghion et al.\textsuperscript{25}, four refractory migraine patients were treated with propofol in the ED. All four patients (age 51 to 62 years) had failed home medications, including serotonin receptor agonists and NSAIDs, for pain relief. Propofol was given as a 1 mg/kg as a slow IV infusion over 1 minute. Three of the four patients ultimately achieved complete resolution of symptoms and the other improved by discharge. One patient was discharged with a heart rate of 48, but no other bradycardia, hypotension, or adverse events were reported. Ward et al.\textsuperscript{23} published a final relevant case series. This report included 15 patients treated for migraine at 22 different ED encounters (age 12–76 years). Propofol was administered as 20 mg IV every 10 minutes until pain resolution. Patients were also able to receive other adjunctive therapies, most commonly ondansetron and dexamethasone. The median treatment duration was 47.5 minutes with a median propofol dose of 75 mg. Four of the 22 cases still experienced pain at the completion of treatment. No adverse effects were reported. The limitations of these case reports and case series include the lack of comparator medications, description of pain severity, small number of treated patients, and extremely low level of evidence inherent to singular descriptive reports.

Based on the success of the published descriptive studies, Soleimanpour et al.\textsuperscript{24} published a double-blind, randomized, active controlled trial to evaluate the effect of propofol on migraine relief compared to dexamethasone in adult patients over the age of 18. In the propofol group (n = 45), patients received a 10-mg IV bolus every 5 to 10 minutes (maximum dose = 80 mg) until the VAS score was less than 2 on an 11-point scale. In the dexamethasone group (n = 45), patients received a 0.15 mg/kg IV bolus (maximum dose = 16 mg). The primary outcome was headache intensity as measured by VAS at baseline and 5, 10, 20, 30, and 45 minutes after treatment initiation. Other medications, such as opioids and NSAIDs, were allowed if no pain reduction was observed. The mean age of patients was 35.7 ± 12.6 years for the propofol group and 36.3 ± 13.4 years for the dexamethasone group. The propofol group was 67\% female while the dexamethasone group was 62\% female. The baseline mean ± SD pain score was 8.0 ± 1.5 vs. 8.1 ± 1.3 (p = 0.712). Other than baseline, pain intensity levels measured at the specified time points were all significantly lower in patients treated with propofol (p = 0.001 or p < 0.001). At 45 minutes, the mean ± SD pain levels were 1.2 ± 1.6 in the propofol group versus 2.9 ± 1.8 in the dexamethasone group (p < 0.001). No significant difference between groups regarding mean oxygen saturation, heart rate, or blood pressure was found. In the propofol group, there were two cases of mild oxygen desaturation (O₂ = 89\%), and these were quickly corrected with the use of nasal oxygen. Other adverse effects reported included one case of slurred speech and 20 cases of mild sedation. The authors concluded that propofol is a safe and effective treatment for acute migraine within the ED and may have a faster rate of response compared to dexamethasone. Some of the major limitations of this study as noted by the authors included the use of convenience sampling and the lack of standard abortive therapy. Other significant limitations included the lack of follow-up for migraine recurrence and baseline patient information, particularly information about failed home or outpatient rescue medication use. It should also be noted that this study allowed other medications to be used if no migraine improvement was observed. The specific medications and the frequency at which this occurred were not reported.

Moshtaghion et al.\textsuperscript{25} conducted a randomized, double-blind, active controlled trial to evaluate the efficacy of propofol for acute migraine treatment compared to sumatriptan in adults (age 18 to 45 years) presenting to the ED. Patients were randomized to receive propofol (n = 45) as a 30- to 40-mg IV bolus followed by a 10- to 20-mg IV bolus every 3 to 5 minutes for a maximum dose of 120 mg or sumatriptan (n = 45) 6 mg subcutaneously once followed by the same dose after 1 hour if the pain score was reduced by less than 4 points. The
mean ± SD age for the propofol group was 33.1 ± 8.1 years and 33.4 ± 7.9 years for the sumatriptan group. The majority of patients were female (74% vs. 77%). Most patients were classified as having common migraine (94% vs. 93%) and failed outpatient medication regimens prior to ED presentation (93% vs. 89%). The primary outcome was pain intensity measured by an 11-point VAS recorded at baseline and 30 minutes, 1 hour, and 2 hours after treatment. Baseline pain intensity scores were 9.1 ± 1.0 for the propofol group and 8.7 ± 1.2 in the sumatriptan group. At 30 minutes, pain intensity was significantly lower for the propofol group (2.6 ± 2.1 vs. 3.7 ± 2.6, p = 0.034). There was no significant difference at 1 hour (2.7 ± 2.6 vs. 2.4 ± 2.3, p = 0.53) or 2 hours posttreatment (1.6 ± 2.0 vs. 1.4 ± 2.0, p = 0.53). Recurrence rate within 24 hours of ED discharge was significantly higher in the sumatriptan group (17% vs. 55%, p = 0.001). There was no significant difference between groups in terms of other symptom improvement, such as photophobia, nausea, and vomiting, at time of discharge. There was, however, a significantly lower number of patients who experienced chest tightness (2% vs. 31%, p = 0.001) and rash at injection site (0% vs. 33%, p = 0.001) in the propofol group. No patients became hemodynamically unstable or experienced oxygen desaturation of less than 90%. The authors concluded that propofol is an effective rescue therapy for acute migraines in the ED setting and associated with fewer adverse effects when compared to sumatriptan. It should be noted that while the propofol had significantly lower pain scores at 30 minutes, there was no significant difference at 1 or 2 hours after treatment. This lack of sustained effect does not provide evidence of benefit over a standard therapy but does suggest that it is a similarly efficacious alternative with a faster onset of action. Interestingly, the migraine recurrence rate within 24 hours of ED discharge was significantly lower in the propofol group. When considering the short half-life of propofol and lack of difference in pain scores at 1 and 2 hours, this is not easily explained. The major limitations of this study include the lack of reporting regarding repeat dosing, method of follow-up, and generalizability based on a single-center study.

**Pediatrics**

Sheridan et al.²⁶ conducted a retrospective cohort study to compare propofol to standard agents for treatment of migraine headaches in pediatric patients aged less than 18 years presenting to the ED. Seven patients who received propofol (mean IV bolus 0.56 mg/kg, mean total dose of 1.71 mg/kg divided over three doses) were matched to seven controls who received diphenhydramine, NSAIDs, and prochlorperazine (n = 7) on the basis of age, migraine prophylaxis, and sex. Groups were similar in terms of baseline age (12.3 ± 3.1 years vs. 14.7 ± 2.1 years), migraine prophylaxis (two of seven patients on prophylaxis in each group) and sex (five of seven patients were female in each group). Baseline 11-point pain VAS was 9.5 with propofol compared to 7 with controls. Following treatment, the mean reduction in VAS was 80% with propofol compared to 61% with control (p = 0.02) with mean length of stay of 122 minutes versus 203 minutes (p = 0.2). One patient in each group returned to the ED within 24 hours. No adverse events were identified. The authors concluded that low-dose propofol may be an option for treatment of pediatric migraine and warrants further study. Several limitations were noted: the possibility that propofol patients more commonly had failed standard therapy, use of diagnosis codes to identify patients, lack of standard diagnostic criteria, possibility that off-label propofol use artificially increased length of stay, and the high level of monitoring involved with use of propofol. The retrospective, observational nature of the study should also be strongly considered as this study design should not be considered sufficient to establish true cause-and-effect relationships. On a related note, baseline median pain score was substantially higher in the propofol group, making it more likely that larger relative improvements in VAS would be observed. Other key limitations clinicians should keep in mind include between-subject variability in standard therapies and controls, as well as the inherent risks of reduced internal validity due to reliance on preexisting data that were recorded for clinical, not research purposes. The limitations of such a small sample size and potential impact of placebo effect in the setting of migraine headache research²⁷ are also substantial; this could also be exacerbated by the distinct appearance of propofol compared to other medications.

Sheridan et al.²⁷ also conducted an open-label, randomized clinical trial to evaluate use of propofol for treatment of acute migraine in pediatric patients aged 7 to 19 years presenting in the ED with a VAS at least 6 out of 10 points. Patients assigned to propofol (n = 30) received up to five IV bolus doses of
0.25 mg/kg (up to 30 mg) until VAS decreased to 4 or less. In the standard-therapy control group (n = 36), patients received ketorolac 0.5 mg/kg IV, diphenhydramine 1 mg/kg IV, and metoclopramide 0.1 mg/kg or prochlorperazine 0.1 mg/kg until the same VAS reduction was achieved. The primary outcome was VAS pain score reduction assessed at 1 hour. Rescue therapy was given at the physician’s discretion. Patient groups were similar in terms of baseline mean age (14.6 ± 2.1 years vs. 14.6 ± 3.0 years), sex (70% vs. 78% female), and mean pain score (7.9 ± 1.1 vs. 8.3 ± 1.4). Patient outcomes were similar in terms of VAS reduction by percent (51% vs. 59%, p = 0.34) and absolute (4.0 vs. 4.8, p = 0.24) measurement, as well as the portion of patients meeting the treatment goal of VAS 4 or less (73% vs. 72%, p = 0.92). Propofol patients were less likely to experience rebound headache (25% vs. 67%, p = 0.01). There were no differences between groups in length of stay or return to the ED. There was a single case of transient oxygen desaturation (O2 = 89%) that did not require intervention in the propofol group. The authors concluded that low-dose propofol was similar to standard therapy for treatment of pediatric acute migraine, with possible benefits on rebound headache. The authors acknowledge several limitations: the possibility of lower enrollment at one site due to lack of tracking mechanisms, lack of standard diagnostic criteria, differences in frequency of VAS measurement between groups (considering individual agents’ pharmacology), exclusion of patients with at least one visit after their index visit, and exploratory nature of the propofol dosing. Additionally, information regarding other rescue therapy was not provided and the lack of blinding should be considered (although patients were not directly notified of which group they were allocated) given high risk for placebo effect in this setting. Although appropriate medications were used in the control group for symptom management, the potential role of serotonin agonists in older children and adolescents was not addressed in the study. A direct comparison to one of these agents potentially would represent a stronger control.

DISCUSSION

In this systematic review, the cumulative evidence for the safety and efficacy of propofol for migraine treatment in the ED was summarized, suggesting that propofol may be an effective therapy for migraine pain based on preliminary evidence from three randomized controlled trials. The small number of patients enrolled in the trials (totaling 181 adults and 66 pediatrics, about half of which actually received propofol) cannot be understated. The retrospective cohort study was also very small. The heterogeneity in dosing, comparator medications, and patient populations among trials, as well as other available evidence, and also seriously reduces the strength of evidence supporting this off-label use. Propofol doses ranged from 10 to 60 mg administered as an IV bolus or boluses. Some studies allowed for repeat doses every 3 to 5 minutes while others only gave a single dose. Furthermore, one study utilized a loading dose. The three randomized controlled trials included active comparators. The adult randomized controlled trials utilized subcutaneous sumatriptan or IV dexamethasone. Sumatriptan is a recommended first-line therapy for acute migraine presentation in the ED, making this agent an acceptable comparator. IV dexamethasone, however, is a suboptimal comparator as it is generally not recommended as standard abortive therapy. Rather, it is often used as an adjunctive therapy to prevent migraine recurrence. Perhaps the strongest comparator was found in the pediatric randomized trial, which utilized combination therapy. Current evidence supports the use of a “migraine cocktail” as an effective therapy in the ED and this may be more reflective of clinical practice. For the adult population, this lack of optimal comparison is certainly a limitation that must be considered when evaluating the overall evidence of propofol therapy for migraine. The duration of migraine, types of medications used prior to presentation, and type of underlying migraine disorder for the randomized controlled trials were also not reported; addressing this information may have given further insight as to the optimal subgroup of patients for maximal efficacy of propofol therapy. Pediatric studies comparing propofol to serotonin receptor agonists were not identified. Finally, given the well-described significant placebo effect observed in treatment of migraine headaches and correlating increase in required sample size, results for these small studies especially the ones that lack an appropriate control, should be viewed as preliminary at best. Overall, although the three trials and single retrospective cohort study scored well on objective evaluation tools, numerous
limitations must be considered when applying these results.

Generalizability is also limited based on these studies. Both adult randomized controlled trials excluded patients who received a triptan or dihydroergotamine prior to ED presentation.24,25 One randomized controlled trial also excluded patients who had received opioids or systemic corticosteroids.24 While these exclusions improve the ability to evaluate the effects of the propofol, they effectively eliminated patients who failed recommended first-line agents from the study. Essentially, patients who are more likely going to be candidates for propofol therapy based on current practice were excluded. It should be noted that in pediatric studies, most patients had no history of treatment.26,27 Additionally, both adult randomized controlled trials and one case series took place at single sites in Iran.21,24,25 Similarly, most patients enrolled in the two pediatric studies were from the same ED.26,27 Out of the 290 patients in this review, 189 were seen at only two EDs.

Another consideration regarding clinical efficacy is migraine recurrence. Multiple patient cases reported recurrent migraine at 24 to 72 hours after ED discharge.20,21,23 In one of the adult randomized controlled trials, the recurrence rate at 24 hours postdischarge was as high as 17%.25 While the evidence supports the use of propofol as a rescue medication for migraine, it does not adequately evaluate long-term effects.

Adverse effects were assessed in all included studies.19–27 Overall, subanesthetic doses of propofol seemed to be well tolerated. Drowsiness or mild sedation was the most common adverse effect among the studies. This is expected based on propofol’s primary use as an anesthetic or sedative agent. Oxygen saturation for a total of three patients declined to 89%, but all were appropriately treated with nasal oxygen with no further complication.21,24 One patient temporarily developed slurred speech.24 No significant bradycardia or hypotension was reported in any of the studies, but the overall small number of total patients most likely does not allow for the identification of rare adverse effects. Risk appeared low in pediatric studies;26,27 however, small sample size suggests that further studies would be needed to rigorously evaluate safety.

Propofol seems to be a promising agent for migraine treatment in the ED with regard to clinical efficacy and safety in the adult population, with mixed results found for pediatrics. Based on the available evidence, propofol is a reasonable last-line or salvage therapy, especially for refractory or intractable migraine patients or in patients who have contraindications to multiple first-line abortive therapies. There may, however, still be significant clinical feasibility issues related to its use. In both randomized controlled trials for the adult population, patients received repeat IV bolus doses every 3 to 10 minutes. These doses were administered by medical personnel based on the patient’s response. One-on-one nursing was provided in one study that utilized up to 1 mg/kg doses. Two of the studies specifically described that patients were monitored with telemetry, automated blood pressure cuffs, and capnography after establishment of the IV line. While subanesthetic doses are not expected to cause significant respiratory depression, these patients still must be closely monitored, especially with regard for oxygen desaturation. For EDs with limited personnel or insufficient monitoring resources, the required conditions for safe, effective propofol use may present too high of a demand.

LIMITATIONS

This review itself has several limitations that should be considered when applying results. First, the formal databases were limited to PubMed and Google Scholar. It is possible that a search of Embase would have resulted in additional relevant articles; however, we minimized this risk by using extensive search terms, hand-searching key journals, screening reference lists of relevant articles, and undertaking a thorough search of trial registries. A limited number of articles are available and these are of lower quality. The modified Jadad system, as well as other clinical trial quality rating systems, has been criticized for being incomplete, among other shortcomings;17 however, we selected it for its objectivity given that we planned to qualitatively, as well as quantitatively, highlight key study limitations. The majority of included studies are descriptive case reports, case series, or cohort studies. Finally, the lack of experimental studies and heterogeneity regarding study design, propofol regimen, nonstandard comparators, unknown or unbalanced cointerventions, and patient populations precluded pooling results in a meta-analysis and warrants caution applying conclusions of this review.

CONCLUSIONS

In summary, propofol may be a comparable rescue agent to current standard therapies for acute migraine.
in adult patients based on the limited clinical results presented in this systematic review. Further evidence, however, is needed as the available data in the adult populations is based on suboptimal comparator agents. The safety of propofol for migraine management in the ED has also not been adequately examined. It could be considered in the appropriate clinical setting when safeguards are in place for desaturations and other possible side effects.

References


Frequency of Abnormal and Critical Laboratory Results in Older Patients Presenting to the Emergency Department With Syncope

Andrew B. Moore, MD, Erica Su, Robert E. Weiss, PhD, Annick N. Yagapen, MPH, Susan E. Malveau, MSBE, David H. Adler, MD, MPH, Aveh Bastani, MD, Christopher W. Baugh, MD, MBA, Jeffrey M. Caterino, MD, MPH, Carol L. Clark, MD, MBA, Deborah B. Diercks, MD, MPH, Judd E. Hollander, MD, Bret A. Nicks, MD, MHA, Daniel K. Nishijima, MD, MAS, Manish N. Shah, MD, MPH, Kirk A. Stiffler, MD, Alan B. Storrow, MD, Scott T. Wilber, MD, and Benjamin C. Sun, MD, MPP

Syncope is a common and costly chief complaint among patients presenting to the emergency department (ED), accounting for 740,000 ED visits annually with an estimated annual cost of $2.4 billion per year in the United States. Syncope presents a diagnostic dilemma for clinicians in the ED since differentiating serious and benign causes of syncope can be challenging, particularly in the older adult. Routine laboratory testing with complete blood count (CBC) and basic metabolic panel (BMP) is commonly ordered for patients presenting to the ED with syncope.
The 2017 American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS) guidelines on the evaluation of syncope in the ED recommend targeted laboratory testing based on history and physical examination, such as prior history of peptic ulcer disease or dark tarry stools. Despite these guidelines, it is common practice to obtain broad panel laboratory testing such as CBC or BMP for ED evaluation of patients with syncope regardless of level of suspicion for abnormalities. Broad panel laboratory testing with CBC and BMP could identify potentially reversible causes of syncope in the older adult including anemia, dehydration, and electrolyte abnormalities. It is not known how frequently routine laboratory testing identifies normal, abnormal, and critical laboratory values in older patients with syncope. The objective of this study was to evaluate the frequency of normal, abnormal, and critical laboratory results from CBC and BMP ordered in older patients presenting to the ED with syncope or near syncope.

We conducted a secondary analysis of a large, multicenter, prospective cohort study (ClinicalTrials.gov identifier NCT01802398) to determine the frequency of abnormal and critical routine laboratory testing at the primary ED visit. The study was approved by the institutional review boards at all sites, and written informed consent was obtained from all participating subjects. Eligible patients were ≥60 years of age with a complaint of syncope or near syncope at 11 academic EDs across the United States. Exclusion criteria were intoxication, medical or electrical intervention to restore consciousness, or inability or unwillingness to provide informed consent or follow-up information. Patients with a presumptive cause of loss of consciousness due to seizure, stroke, or transient ischemic attack or hypoglycemia were also excluded. For this analysis, we also excluded patients who did not have a CBC or BMP performed.

All patients underwent history and physical examination, laboratory testing at the discretion of the treating physician, and 12-lead EKG testing. Patient disposition was directed by the treating clinical providers. We evaluated the following routine laboratory tests: hematocrit, glucose, sodium, potassium, bicarbonate, blood urea nitrogen, and creatinine. We defined abnormal ranges for the BMP using standard reference ranges. We determined abnormal hematocrit ranges based on preexisting syncope literature. We determined critical values by an institutional laboratory protocol. The primary outcome is the proportion of abnormal and critical laboratory values obtained from CBC and BMP laboratory testing.

We present data as means with standard deviations (SD) or medians with interquartile ranges. We tested independence between categorical variables with chi-square or Fisher's exact test. We performed statistical analyses using the R package. All p-values are two-sided and we considered those ≤ 0.05 to be significant.

There were 6,930 subjects that met eligibility criteria, of whom 3,686 (53.2%) consented and were enrolled into the primary study. Of the 3,686 enrolled subjects, 105 subjects had no serious outcome and were lost to follow-up or withdrawn from the study, resulting in a base cohort of 3,581 subjects. There were 3,557 patients (99.3%) who had CBC or BMP laboratory testing performed in the ED, representing the cohort for this study. Twenty-four subjects (0.7%) with a mean (±SD) age of 68.4 (±6.8) years (p = 0.015), but otherwise similar baseline demographics to the study cohort, had missing laboratory values and were excluded from the analysis (Data Supplement S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13096/full).

Study subjects had a mean (±SD) age of 72.8 (±9) years, 1,835 (51.6%) were male, and 1,722 (48.4%) female. Compared to patients who had normal laboratory testing, those who had abnormal laboratory testing or critical laboratory testing were more likely to have a history of congestive heart failure, coronary artery disease, or arrhythmia; be on diuretics, beta blockers, or calcium channel blockers; and have an abnormal ECG or hypotension on initial vital signs and to be hospitalized.

Of all laboratory results collected, 69.9% were normal, 29.9% were abnormal, and 0.7% were in the critical range (Table 1). We found 323 patients (9.1%) had entirely normal laboratory results, 3,080 patients (86.6%) had at least one abnormal, but no critical, laboratory results, and 154 patients (4.3%) had at least one critical laboratory result (Table 1). Abnormal laboratory values were most commonly elevated blood glucose (72.9%), elevated blood urea nitrogen (44.4%), hyponatremia (21.7%), hypokalemia (16.7%), and anemia (8.4%; Table 1). The most common critical laboratory results were serum
We found that in a large cohort of older adults with syncope, abnormal laboratory values were frequently identified in laboratory screening of this population with CBC and BMP. Critical laboratory values on laboratory testing with CBC and BMP occurred in 4.3% of this population. Current AHA/ACC/HRS guidelines indicate routine and comprehensive laboratory testing is not useful in the evaluation of syncope.4 Our findings suggest otherwise in a cohort of older adults. In patients ≥ 60 years of age, with syncope or near syncope, critical laboratory values occurred at a rate above the generally accepted risk threshold for ED presentations such as pulmonary embolism.8 In this population, laboratory testing with CBC and BMP is likely to provide abnormal results with minimal increased risk to the patient.

Professional society guidelines recommend a minimal role for diagnostic testing in the evaluation and management of syncope.4 However, these guidelines are primarily based on literature of small study cohorts and included young, healthy individuals with mean age of 41.3 and 63.1 years, respectively.9,10 Young, healthy patients are much more likely to have a vasovagal syncopeal event and it is possible that inclusion of these patients diminished the value of broad-panel blood testing in the evaluation of syncope in these studies. Further, the small cohort sizes and wide age range of patients suggests that these early syncope studies may not accurately present the utility of laboratory screening in older adults with syncope. We limited enrollment to patients ≥ 60 years of age, or older, and our mean (±SD) patient age was 72.8 (±9) years. Our data suggest that patients ≥ 60 years have frequent abnormal laboratory findings on CBC and BMP and occasional (4.3%) critical laboratory findings. Our research demonstrates that routine laboratory testing in older adults with syncope may affect disposition decisions in the ED or identify needs for ED intervention.

The major limitation of this study is that laboratory tests occurred at an index ED visit without comparison to historical laboratory results for each patient. Second, our study cohort had a small percentage of subjects with missing laboratory values that were not included in the analysis. Third, laboratory processing errors or spurious laboratory results due to hemolysis or dilution may have contributed to our high proportion of abnormal tests. Fourth, further stratification of laboratory values may increase the clinical significance of laboratory results. We selected abnormal and critical laboratory value ranges defined by existing literature and institutional guidelines, respectively. In some

<table>
<thead>
<tr>
<th>Table 1 Frequency of Critical, Abnormal, and Normal Laboratory Results Obtained from CBC and BMP Laboratory Testing in Older Adults with Syncope</th>
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<tbody>
<tr>
<td><strong>Clinical Laboratory (Value)</strong></td>
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<tr>
<td>Total percentage of all laboratory values</td>
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<tr>
<td>Normal</td>
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<tr>
<td>Abnormal</td>
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<tr>
<td>Percentage of patients with laboratory results</td>
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<td>At least one abnormal, but no critical</td>
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<td>Hct (%)</td>
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<td>50%&lt; Hct &lt; 60%</td>
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<td>&gt; 60%</td>
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<td>Glucose (mg/dL)</td>
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<td>Sodium (mmol/L)</td>
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<td>120&lt; Na &lt; 136</td>
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<td>136&lt; Na &lt; 144</td>
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<td>144&lt; Na &lt; 160</td>
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<td>Potassium (mmol/L)</td>
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<td>2.5&lt; K &lt; 3.7</td>
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<td>3.7&lt; K &lt; 5.2</td>
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<td>5.2&lt; K &lt; 6.0</td>
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<td>Bicarbonate (mmol/L)</td>
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<td>10&lt; CO2 &lt; 20</td>
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<td>20&lt; BUN &lt; 100</td>
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<td>Cr (mg/dL)</td>
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<td>1.2&lt; Cr &lt; 4.0</td>
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<td>&gt; 4.0</td>
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BMP = basic metabolic panel; BUN = blood urea nitrogen; CBC = complete blood count; Cr = creatinine.
instances, such as glucose, our abnormal laboratory values may include a range that is not clinically relevant. Fifth, although we found that increased medication use, medical comorbidities, ECG abnormalities, and hypotension were associated with abnormal and critical laboratory results, this descriptive study did not assess outcomes based on laboratory results. Sixth, our study included only adults ≥ 60 years and may not be generalizable to younger patients. Finally, our population was predominately from academic medical centers, possibly resulting in higher medical complexity and comorbidities than the general population.

In conclusion, in a large cohort of adults ≥ 60 years of age with syncope or near syncope, laboratory testing with CBC and BMP commonly identified nonnormal laboratory values and identified critical laboratory values in one in 25 patients.

References


Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13906/full
Hot Off the Press: Please Stop, Prescribing – Antibiotics for Viral Acute Respiratory Infections

Christopher Bond, MD¹, Justin Morgenstern, MD², Corey Heitz, MD³, and William K. Milne, MD⁴

BACKGROUND

Inappropriate antibiotic use exposes patients to opportunistic infections, accelerates the development of antibiotic resistant bacteria, and leads to adverse drug events.¹ Acute respiratory infections (ARIs) are a major cause of unnecessary antibiotic use. Emergency departments (EDs) in the United States write 10 million antibiotic prescriptions each year, approximately half of which are inappropriate.²–⁴ Given these risks, strategies to reduce inappropriate antibiotic use in the ED and urgent care center (UCC) are needed.

Despite recognizing the need for antibiotic stewardship by EDs and emergency providers, this has not led to practice change.⁵,⁶ Providers in the ED and UCC setting are faced with numerous challenges that may limit change, including frequent interruptions, boarding and overcrowding, frequent patient handoffs, and the need to see high volumes of patients.⁷–⁹

There is evidence both in the medical literature and in economic theory to support using a package of feedback, nudges, and peer comparisons to improve prescribing outcomes. This has been shown to reduce unnecessary antibiotic prescribing in primary care, and in one study of peer comparisons in outpatient clinics and doctor’s offices, these improvements were sustained for at least 12 months after the interventions were completed.¹⁰–¹²

ARTICLE SUMMARY

This study asks if an enhanced intervention is more effective than an adapted intervention in reducing inappropriate antibiotic prescribing for ARIs by clinicians in an ED/UCC setting. The adapted intervention incorporated strategies from the Centers for Disease Control and Prevention’s Core Elements for Outpatient Antibiotic Stewardship, including provider and patient education, a physician champion, and departmental feedback. The enhanced intervention added audit and feedback, peer comparisons, and behavioral nudges to the adapted intervention. The primary outcome was the rate of inappropriate outpatient antibiotic prescribing for ARIs that were deemed antibiotic nonresponsive. The secondary outcome was the difference between the enhanced and adapted intervention in antibiotic prescribing.

QUALITY ASSESSMENT

Overall this was a well-done pragmatic, cluster-randomized trial performed in five adult and pediatric EDs.
and four UCCs across three academic health systems within the United States. Randomization of the sites was stratified by study site rather than by individual physician. According to the authors, this was to reduce contamination, wherein individual providers randomized to different arms could influence each other in unpredictable ways. Furthermore, with the enhanced intervention, specific posters signed by ED/UCC providers unblinded them to group allocation.

Another concern is the lack of a contemporaneous control group in this study. This was difficult because participating institutions had incentives to rapidly deploy antibiotic stewardship programs, so there was no buy-in to be a control site for the study duration. A stepped-wedge cluster-randomized design with each site receiving the intervention in a prescribed order, with those not yet receiving the intervention acting as controls, is currently being studied by the authors.

The EDs/UCCs in this study also had low inappropriate prescribing rates at baseline (2.1%–7.4%). As a result, the effectiveness of the interventions in this study may have been less impressive than at many other sites. A final concern is the variety of clinicians providing care in these settings, which included adult and pediatric emergency physicians, advanced care practitioners, internists, and pediatricians. Thus, generalizability to some practice settings may be limited.

**KEY RESULTS**

The primary outcome of inappropriate antibiotic prescribing for ARIs saw a decrease from 6.2% (95% confidence interval [CI] = 4.5% to 7.9%) to 2.4% (95% CI = 1.3% to 3.4%). After provider, seasonal, and institutional fixed effects were adjusted for, there was a significant year-over-year reduction from baseline to intervention period (odds ratio = 0.67, 95% CI = 0.54–0.82) with an absolute effect size of 0.7% (95% CI = 0.2% to 1.2%). The secondary outcome showed a nonsignificant (p=0.06) difference between the reduction in inappropriate antibiotic prescribing between the enhanced and standard intervention groups.

**AUTHORS’ COMMENTS**

This project was guided by implementation science, which is a rigorous, theory-driven approach to practice improvement. It relies on careful deliberation of the local conditions when preparing for an intervention (which may modify what you do), followed by a mixed-methods approach to conducting the intervention and measuring several outcomes related to implementation processes. We think it holds great promise for elevated local quality improvement projects to interventions worthy of knowledge translation.

**TOP SOCIAL MEDIA COMMENTARY**

On Twitter, Rick Barnett (@DrRickBarnett) commented:

Interesting. How does this relate to about a decade ago when time-to-prescribe abx in ED for ARI was the goal or “best practice” which resulted in over-prescribing practices?

Study author Jason Doctor (@jasndoc) responded:

We targeted antibiotics that were prescribed for viral infections. This is to be distinguished from appropriate and timely use of antibiotics for bacterial infections.

As did lead author Kabir Yadav (@DrKabirYadav):

I was there - abx given in triage to meet a poorly-conceived quality metric. Better knowing who benefits and who is harmed is key to any abx stewardship effort (we focused on viral ARIs). Goal is abx for the right diagnosis, right patient, right drug, right dose, right duration.

**TWITTER POLL**

How’s your emergency department’s use of antibiotics for acute respiratory infections? ncbi.nlm.nih.gov/m/pubmed/31215... @SAEMonline @AliRaja_MD @Rick_Pescatore #sgemhop

Just right: 37%
Not enough: 5%
Too much: 58%

65 votes - Final results
10:32 AM - Jul 30, 2019 - Twitter for iPhone
Implementing strategies to reduce inappropriate antibiotic prescribing in the ED/UCC are feasible and likely effective. However, there is no evidence from this study that an enhanced intervention using additional audit and feedback, peer comparisons, and behavioral nudges will be more effective than an adapted intervention.

References


Use of the Clinical Examination in the Diagnosis of Cardiac Syncope

Kathryn Wiesendanger, and Daniel K. Nishijima, MD, MAS

**Summary heading**

While no single finding or test rules cardiac syncope in or out, several findings may increase or decrease the probability of cardiac syncope.

**Patient history:**

Age at first syncopal episode older than 35 years = 3.3
History of atrial fibrillation or flutter = 7.3
Known severe structural heart disease = 3.3 to 4.8
Dyspnea prior to syncope = 3.5
Cyanotic during syncope = 6.2

**Diagnostic tests:**

- High-sensitivity cardiac troponin T > 42 pg/mL = 5.1
- High-sensitivity cardiac troponin I > 31.3 pg/mL = 5.4
- NT-proBNP ≥ 210.5 pg/mL = 47
- NT-proBNP > 1966 pg/mL = 5.8
- BNP > 302 pg/mL = 6.3

**Multivariable evaluation:**

- Heart disease, abnormal ECG, or both = 2.3
- EGSYS score 3 or more = 2.8 to 3.3
- Vasovagal score less than –2 = 1.7 to 8.6

**Negative findings for cardiac syncope (LR-)**

- Age at first syncopal episode 35 years or younger = 0.13
- Normal cardiac troponin T or I ≤ 0.15 to 0.39
- Normal BNP level = 0.16 to 0.21

**Continued**

**NARRATIVE**

Syncope or transient loss of consciousness is a common problem seen in the emergency department (ED), accounting for 1% to 1.5% of ED visits annually. Cardiac syncope caused by cerebral hypoperfusion secondary to cardiopulmonary events such as arrhythmia or structural heart disease, accounts for 5% to 21% of syncope events. Cardiac syncope is associated with an increased risk of premature death and cardiac events. It is therefore important for emergency providers to differentiate cardiac syncope from other causes.

This systematic review by Albassam et al. evaluated patient characteristics, physical examination findings, and diagnostic tests to identify cardiac causes of syncope. The authors searched the MEDLINE, Embase, CINAHL, and Cochrane databases, selecting 11 studies that met inclusion and exclusion criteria. Each study included at least 10 subjects aged 12 years or...
older, for a total of 4,317 patients. Studies were assigned levels of evidence developed for the Rational Clinical Examination series.6

Several historical factors were associated with an increased likelihood of cardiac syncope including age at first syncopal episode 35 years or older; history of atrial fibrillation or flutter; known severe structural heart disease; dyspnea or chest pain prior to syncope; and witnessed cyanosis during syncope. An elevated cardiac troponin T or I and an elevated B-type natriuretic peptide (BNP) both modestly increased the probability of cardiac syncope.

Factors that decreased the probability included age less than 35 years at first syncopal episode; normal cardiac troponin T or I; and normal BNP. Combinations of findings such as Evaluation of Guidelines in Syncope Study (EGSYS) score ≥ 3; vasovagal score < −2; and abnormal electrocardiogram, heart disease, or both were more useful when absent than when present.

CAVEATS

The results of this review should be interpreted cautiously. Included studies generally defined cardiac syncope based on cardiologist judgment. Five of 11 studies included specialty referral populations or inpatients, leading to the potential for spectrum bias. Applying these results to a general ED population might lead to additional testing or interventions in patients who have lower risk of cardiac syncope than the studied population. Misclassification may have further skewed the results as patients with unexplained syncope were excluded from several studies. Many of the clinical findings resulted from single studies. Studies often included a wide age range of patients despite the incidence of syncope, related ED visits, and serious outcomes increasing sharply after the age of 60.7

Cardiac biomarkers such as troponin or BNP testing appear to be an attractive diagnostic option, however, they did not rule in or rule out cardiac syncope. Moreover, these cardiac biomarkers were likely used to diagnose cardiac syncope leading to incorporation bias. ACEP clinical policy, appreciating these limitations, suggests a risk stratification approach focusing on patient history and physical examination to avoid unnecessary testing and hospital admissions.1

In summary, the accurate diagnosis of cardiac syncope is helpful in determining an appropriate plan of care. While no single variable can independently diagnose or exclude cardiac syncope, several clinical findings may be used cohesively to help guide health care providers.

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Risk of Recurrent Venous Thromboembolism and Bleeding in Cancer Patients Treated With Direct Oral Anticoagulants Versus Low-molecular-weight Heparin

Brit Long, MD1, Alex Koyfman, MD2, and Michael Gottlieb, MD3

Summary heading

Among cancer patients with acute venous thromboembolism (VTE), direct oral anticoagulants reduce recurrent VTE with a possible increased risk of major bleeding when compared with low-molecular-weight heparin (LMWH)

NNT color recommendation

Yellow (unclear if benefits)

Benefits in NNT

1 in 41 were helped (recurrent VTE prevented)

Benefits in percentages

2.44% were helped (lower risk of recurrent VTE)

Harms in NNH

No one was harmed (no significant difference in risk of major bleeding compared to LMWH)

Harms in percentages

No one was harmed

Efficacy endpoints

Recurrence VTE

Harm endpoints

Major bleeding

Who was in the studies

11 studies of 4,509 patients (1868 patients receiving DOACs and 2,641 patients receiving LMWH)

NARRATIVE

Venous thromboembolism (VTE) occurs in up to 30% of patients with cancer.1,2 Prior guidelines have recommended low-molecular-weight heparin (LMWH) for 3 to 6 months as first-line therapy in cancer patients with newly diagnosed VTE.3–5 Unfortunately, LMWH is associated with poor compliance due to the need for subcutaneous injection.6,7 Direct oral anticoagulants (DOACs) have been increasingly used for the treatment of VTE, are administered orally with no requirement for regular laboratory monitoring, and may have fewer drug–drug interactions as compared with warfarin, despite DOACs possessing a greater cost compared to other therapies. Several more recent guidelines, including the National Comprehensive Cancer Network (NCCN) and International Society...
on Thrombosis and Haemostasis (ISTH), recommend DOACs, based on limited data. However, other guidelines including the American Society of Clinical Oncology still preferentially recommend LMWH, and DOAC efficacy and safety remain controversial in patients with cancer and acute VTE when compared to LMWH.

This systematic review and meta-analysis included studies comparing DOACs with LMWH for the treatment of VTE in patients with cancer. The primary outcomes were VTE recurrence and major bleeding in patients with cancer receiving DOACs or LMWH. Major bleeding was defined as clinically overt bleeding associated with a decrease in hemoglobin of 2 g/dL or more, requiring transfusion of 2 or more units of blood, occurring in a critical site (e.g., intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular with compartment syndrome), or fatal bleeding as per ISTH criteria. Authors conducted subgroup analyses based on study design, specific medication, and duration of follow-up.

The authors identified 11 relevant studies (n = 4,509), with two randomized controlled trials (RCTs; one trial each evaluating edoxaban and rivaroxaban) and nine observational cohort studies (six studies evaluating rivaroxaban and three studies other DOACs). The follow-up period was ≥ 1 month in all studies. DOACs reduced VTE recurrence from 11.45% to 9.01% (absolute risk reduction [ARR] = 2.44%), with a relative risk (RR) of 0.72 (95% confidence interval [CI] = 0.60–0.85) and number needed to treat (NNT) of 41 compared to LMWH. Subgroup analyses of RCTs and observational studies demonstrated a consistent reduction in VTE recurrence with DOACs. Overall, there was no statistically significant difference in major bleeding, including intracerebral, retroperitoneal, and intraspinal. Subgroup analyses of only observational studies, length of follow-up (6 and 12 months), and rivaroxaban also revealed no increased risk of bleeding. However, subgroup analysis of only RCTs did find increased risk of major bleeding with DOACs (RR = 1.78, 95% CI = 1.11–2.87).

CAVEATS

This meta-analysis possesses several limitations. The two RCTs demonstrating increased rates of major bleeding with DOACs primarily involved the gastrointestinal (GI) tract. However, both studies included a large number of patients with GI malignancies, and these studies were industry-sponsored. It is unclear whether DOACs may be safer in patients without GI tract malignancies, and further data are needed. The definition of active cancer was not consistent in the included studies, and not all studies classified the cancer types or stages. Many studies also did not specify the type or the chronicity of VTE. Included studies evaluated different DOACs and LMWH comparators. This meta-analysis included predominately observational studies, which can introduce confounders and selection bias. While these studies demonstrated incidences of recurrent VTE similar to RCTs, differences in the baseline characteristics of patients and potential unidentified confounders can introduce bias. Follow-up and duration of therapy varied in the included studies, producing a potential source of heterogeneity.

This meta-analysis suggests that cancer patients who receive DOACs have significantly reduced risk of VTE when compared to LMWH, with the best evidence found with rivaroxaban. The risk of major bleeding is less clear, as data across all studies fail to show a difference, but RCT data suggest increased harm. In the context of this study, DOACs remain a viable option to reduce risk of VTE in cancer patients, particularly among patients at low risk of bleeding. Their oral administration and lack of required monitoring is patient-centric and likely improves compliance. We have assigned a color recommendation of yellow (unclear if benefits) based on the benefit for reduction of VTE, but potential increased risk of major bleeding reported in RCTs. Larger, high-quality RCTs are needed to establish with more certainty the promising benefits suggested by these data, as well as further study of the effects of cancer type and specific DOAC medication.

REFERENCES


Are There Long-term Consequences to Psychological Stress During a Medical Event?

The experience of being treated for an acute medical event is a frightening and stressful experience for many patients. Understanding the impact of psychological stress during medical events is important, not only for our understanding of the potential development of short- and long-term adverse psychological outcomes but also for its implications with broader health and recovery. In their recent study, Moss et al. assessed patient perceived fear (e.g., “threat”) during evaluation of a life-threatening cardiovascular or respiratory event. In this sample of 99 patients, they found that almost all (98%) patients who completed the assessment reported some degree of perceived threat on a validated screening measure, while 72% of individuals reported posttraumatic symptoms in relation to their ED visit at follow-up. (median [range] score = 7 [0-30]).

The results of this study build on previous work in the emergency department setting noting the association of psychological stress and development of sustained psychological symptoms in medically ill patients, although the prevalence of posttraumatic stress disorder (PTSD) symptoms reported at follow-up in this sample appear significantly higher than previously published rates of PTSD following cardiac event. A meta-analysis summarizing 24 studies and 2,383 patients found an aggregated prevalence estimate of PTSD in one in six survivors of an acute coronary syndrome, with similar incidence of PTSD noted in survivors of other life-threatening conditions such as stroke. The authors reported their findings of PTSD symptoms at follow-up using raw scores on the PCL-5, a widely used and validated instrument for posttraumatic symptom assessment. While details were provided in the article regarding distributions for the initial threat assessment, further details on the frequency and distribution of the subsequent PCL-5 scores would have provided readers additional information on patients’ levels of anxiety and if the symptom severity reported by patients approached cutoff scores, suggesting possible clinical PTSD. The reported prevalence of 72% of patients endorsing some PTSD symptoms following a life-threatening event is tempered by the relatively low median score of PCL-5 of patients reporting PTSD symptoms at follow-up (i.e., 7), where cutoff scores of 30 and above commonly conceptualized as probable PTSD. Building on this, a broader clinical question remains unanswered: even if patients following acute medical events may endorse anxiety symptoms, how does one tease apart what is likely an anticipated and expected psychological reaction to having survived an acute medical event to manifestations of an adverse and maladaptive process that would benefit from potential intervention? Additionally, in this sample, a diverse group of cardiac and pulmonary medical events were aggregated as “life-threatening illness.” Are the psychological processes experienced during specific medical events like an acute coronary event particularly high risk for the development of sustained psychological symptoms, compared to other events, such as a chronic obstructive pulmonary disease exacerbation? These questions remain unanswered by this study and will likely necessitate a series of longitudinal prospective studies of large cohorts of patients with inclusion criteria careful to distinguish between samples of patients with various

BC was supported by federal grant R01 HL141811
The author has no potential conflicts to disclose.
medical events and an extensive range of measures and outcomes drawn from diverse biopsychosocial candidate factors in survivors. Several active federally funded prospective studies are currently under way examining the development of psychological and somatic symptoms in ED survivors of acute events from trauma (U01 MH110925: AURORA), ischemic stroke (HL 141811), and cardiac events (HL 132347). Data from these projects and others will complement the work presented by Moss et al.1 and build on our understanding of psychological recovery following acute medical events.

In their primary analysis, Moss et al.1 found that there was no significant association with environmental factors, such as ED crowding and subsequent PTSD symptom severity. Other studies, with larger samples, have found a correlation between environmental factors such as ED crowding and PTSD severity, using different operationalizations of crowding, such as the EDWIN score.6 Given the relatively small effect sizes for this previously reported difference, the modest sample of this study (n = 99) may have been underpowered to detect possible significant changes in this secondary aim of their study. Future studies evaluating this relationship using a variety of measures of operationalized environmental factors across larger samples may assess the stability and reproducibility of any such findings. Additionally, the inclusion of ED crowding in this study, also raises the concept that, beyond state and trait factors attributed to the patient, other aspects of the acute care experience itself may influence the development of adverse psychological reactions during the event. For example, past studies have noted the association of posttraumatic stress symptoms in survivors of acute medical events in other acute care environmental factors not included in this study, including hallway care,7 maladaptive patterns of social support,8 preexisting depressive states,9 and clinician–patient communication.10 Integrating and exploring the potential links between these environmental factors, with preexisting state and trait variables, may lead to the nuanced understanding and appreciation of the hospitalization experience experienced by patients being treated for a life-threatening event.11

Emergency providers are clinicians skilled at managing life-threatening conditions across a range of physiologic organ systems. Understanding the psychological reactions experienced by patients during such events provides another layer of information regarding the acute experience of patients treated in the ED. The work by Moss et al.1 is an important contribution to our understanding of the sustained effects that psychological stress during acute medical events may have on long-term patient well-being. Work building on this study will improve our understanding of these effects and ideally lead to the identification of modifiable targets of interventions to improve patient recovery in the near- and long-term setting.

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Supervising Editor: Zachary F. Meisel, MD, MPH, MSc

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Acute pulmonary embolism (PE) is a “can’t miss” diagnosis in the emergency department (ED) that mandates investigation should clinical suspicion be aroused. As the growing availability of multidetector-row computed tomography pulmonary angiography (CTPA) has decreased the threshold for testing, the prevalence of PE has rapidly increased to as many as 112.3 cases per 100,000 U.S. adults. For PE management, there remains considerable debate regarding inpatient versus outpatient treatment, which patients benefit from advanced therapies, and who requires long-term anticoagulation. Nevertheless, therapeutic anticoagulation alone remains the mainstay of acute PE management for the vast majority of patients.

Professional guidelines recommend prompt initiation of anticoagulation in acute PE, even before the diagnosis is confirmed in those highly suspected of the disease. Rapid initiation of therapeutic anticoagulation also improves patient outcomes. In a study of 400 consecutive patients diagnosed with acute PE in the ED, administration of therapeutic anticoagulation was associated with lower in-hospital and 30-day mortality rates. Achieving a therapeutic activated partial thromboplastin time (aPTT) within the first 24 hours led to 4.1 and 9.2% absolute rate reductions in in-hospital and 30-day mortality rates, respectively.

The majority of patients with acute PE are still treated with heparin products, most commonly intravenous unfractionated heparin (UFH) or a subcutaneous low-molecular-weight heparin (LMWH). In the Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry (EMPEROR), UFH was the most commonly administered anticoagulant in the ED (47.8% of participants), and this rate exceeded that of all LMWHs or fondaparinux combined (37.0%). Commonly cited reasons for using UFH as a first-line agent include its rapid onset, short half-life, ability to “turn off” in case of thrombolysis, invasive procedure, or bleeding and the availability of a reversal agent.

Despite these explanations, the preference for UFH is at odds with professional guidelines and published data. UFH, in contrast to LMWH, is notorious for its unpredictable pharmacokinetics from its small volume of distribution and variable half-life due to a wide-ranging molecular weight, two-phased elimination, and extensive binding to plasma proteins. As a result, UFH is within the therapeutic range only 22% of the time in patients with acute PE. Current guidelines recommend LMWH or fondaparinux over UFH in the majority of patients. The only exception is individuals with high-risk PE, defined as those with hemodynamic instability. Fewer than 5% of patients with PE are classified as high risk by this definition. Routine use of either systemic or catheter-delivered thrombolysis in low- or intermediate-risk PE is not indicated, so ubiquitously administering UFH in anticipation of advanced therapies is unwarranted.

This continued reliance on UFH also exposes patients to an increased risk of bleeding. In an observational study of 2,610 patients (3,066 hospitalizations) receiving therapeutic anticoagulation for any indication, UFH was associated with a nearly fivefold increased risk of moderate or severe bleeding.
compared to LMWH. Similarly, in a meta-analysis of 1,951 patients with PE from 12 randomized controlled trials, UFH was associated with a 49% increased risk of bleeding complications compared to LMWH, although this did not reach statistical significance.

The current issue of Academic Emergency Medicine includes a contemporary analysis of UFH for acute PE in the setting of PE Response Team (PERT) consultation that adds importantly to this evidence base. This study included all patients at Massachusetts General Hospital with an acute PE and subsequent PERT activation over a 4.5-year period from 2012 to 2017. The PERT is a multidisciplinary team consulted for known and suspected PE felt to be at high risk. This consultation system rapidly facilitates evaluation of the patient, discussion of care options involving multiple specialties, and ultimately delineation of a cohesive care plan.

The present study analyzed patients treated with UFH according to a hospital-wide ordering template embedded in the electronic medical record. Two dosing options were available: standard dosing, which involved a bolus of 80 U/kg followed by an infusion of 18 U/kg/hour, or an infusion-only regimen, which consisted of an infusion at 18 U/kg/hour without a bolus. Heparin dosing was titrated to target an aPTT of 60 to 80 seconds with repeat laboratory measures typically drawn every 6 hours. The primary outcome was the proportion of individuals with an aPTT within this range during each 6-hour time period of treatment.

Of the 716 patients with PERT activation, 505 (70.5%) were treated with UFH and were otherwise eligible. The median age was 66 years with a median BMI of 29.3 kg/m². As intended with PERT activation, this was an ill population. Nearly half of participants had evidence of right heart strain on CTPA, this was an ill population. Nearly half of participants had evidence of right heart strain on CTPA, consisting of an infusion at 18 U/kg/hour without a bolus. Heparin dosing was titrated to target an aPTT of 60 to 80 seconds with repeat laboratory measures typically drawn every 6 hours. The primary outcome was the proportion of individuals with an aPTT within this range during each 6-hour time period of treatment.

Using UFH over LMWH to reduce the risk of bleeding is also unwarranted. More than one-third of individuals on UFH had aPTT values in the supratherapeutic range, and a dosing regimen without UFH bolus performed even worse than one with a bolus. Such a strategy falsely reassures clinicians while unnecessarily exposing patients to further risk.

As the authors note, there are several limitations to the present analysis. This was a single-center study at
translational and clinical cardiovascular research center, division of cardiovascular medicine, department of medicine, vanderbilt university medical center, nashville, tn

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REFLECTIONS

The Stray Bullet Project

July 7, 2017, 11:50 PM—American University of Beirut Medical Center, Beirut, Lebanon.

I was examining a patient in the pediatric intensive care unit (PICU) when I received the call. I ran to the emergency department (ED) to see Adam. He was intubated, waiting for transfer to the PICU.

Adam was a beautiful 7-year-old boy with spiky hair and blond highlights. He was rushed to the ED by his parents, still in his tailored suit and black bowtie after collapsing while playing the tambourine at his uncle’s engagement party. He arrived pulseless; circulation returned after two cycles of cardiopulmonary resuscitation (CPR), his physical exam was nonfocal except for a pinpoint hole, as small as the tip of a pencil, on the left side of his head. Imaging revealed a penetrating bullet injury to the brain and the spinal cord. The bullet had entered from the left parietal brain, traveled through the corpus callosum and the medulla, and lodged behind T1 and T2 in the subarachnoid space.

When Adam’s parents were informed of their son’s diagnosis, the word “bullet” rippled across the room. The moment of comprehension was palpable, the room transformed into a scene from a horror movie: his mother and grandmother burst into tears, kissing his hands and face, his father sat on a chair next to them breathing heavily and listening to his uncle’s screams: “I will find that shooter and send him to jail.”

People take for granted the very poignant line drawn by the trajectory of a stray bullet. In an instant, a celebration irrevocably becomes a tragedy. Adam was another victim of a senseless tradition: celebratory gunfire. It is imperative to note that firearms are readily available in Lebanon—a country torn by past civil wars—and have become ubiquitous during celebrations and tragedies alike: a shower of hailing bullets to mark an engagement, a funeral, election results, and high school graduations. People fill the skies with bullets that eventually come back down claiming innocent lives, often children’s, on their way.

Stray bullet injuries have become an epidemic all over the world. Since 2016, at least seven reported victims have died from stray bullets shot during weddings, engagement parties, political speeches, elections, and official exams results in Lebanon, annually.1 Failure to enforce already lenient antifirearm and shooting laws has made ownership, carrying, and shooting of firearms a common occurrence.2

July 15, 2017, 12:00 PM: Adam succumbed to his injury 6 days later. My attending physician and I went straight to the second stage of grief: anger. Something had to be done. Our rage compelled us to advocate for change. Along with two pediatric residents, we launched the Stray Bullet Project. This project aims to 1) raise awareness about the brutality of celebratory gunfire, 2) encourage the Lebanese to cooperate with internal security forces to trace shooters, and 3) (re)enforce the laws. The last has been our greatest challenge.

After months of research, we were finally able to get some statistical data from the Lebanese Internal Security Forces. According to the data, there were approximately seven casualties and 167 injuries each year (2016, 2017, 2018), 50% of those injured were children, and three of the seven were children below the age of 10.1 These numbers are an underestimation, given most injuries remain unreported.

Despite many challenges, our team remains motivated; we have continued our campaign by telling Adam’s story at grand rounds, at national and international conferences, and by lobbying for change with politicians. The Stray Bullet Project has been adopted as one of the American University of Beirut’s corporate responsibility projects. We even collaborated with a local NGO on behavioral economics to brainstorm on ways we could spread awareness and change behaviors around celebratory gunfire. Our hope is for our message to permeate younger generations, who will work with us toward an end to this archaic practice once and for all. After all, our role as physicians—especially as pediatricians—is not only limited to diagnosis and treatment of illness and
Our mission provides us with unique opportunities to offer guidance through awareness and prevention, ultimately improving the health of individuals, populations, and even nations. We hope that our efforts result in policy and law change regarding the tradition of shooting during public occasions—a practice that has claimed lives of children and adults in a country barely recovering from a history of conflict.

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