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ABSTRACT

Introduction. The purpose of this study was to assess gender-based mistreatment during medical education recalled by women who attended medical school between 1948 and 1975 and their perspectives on the #MeToo movement.

Methods. Methods included a qualitative analysis of video-recorded structured interviews.

Results. The 37 participants graduated in classes of 2-20% women. They described pervasive, multi-faceted gender-based mistreatment during training. Twenty (54%) disclosed personal experience of serious sexual mistreatment. Interviewees stressed that attitudes and behaviors toward women and trainees, now regarded as unacceptable, were previously widely accepted or tolerated. The majority (86%) expressed overall positive opinions of their training. Twenty-eight (76%) supported the #MeToo movement, four (11%) expressed negative opinions, and five (13%) were ambivalent or unwilling to comment. Seventeen (46%) were concerned that #MeToo damaged working relationships, twelve (32%) were concerned about overreach, and eight (22%) about false accusations.

Conclusions. This group of older female physicians reported extensive experience of gender-based mistreatment and strong support of #MeToo. Nevertheless, about one quarter of the group did not support the #MeToo movement and even supporters expressed high rates of concern about the movement going too far, falsely accusing men of inappropriate behavior, and damaging working relationships. The interviewees did not want their medical training to be characterized as entirely negative, or to be portrayed as victims.

INTRODUCTION

The #MeToo and related movements have highlighted sexual harassment of women in the workplace and renewed interest in the mistreatment of women in medicine.15 Studies estimate that 40-70% of female medical students experience sexual harassment, predominantly from male faculty or staff members.5,8 These rates are up to twice those reported for trainees in other scientific fields.67 The prevalence could be even higher as gender-based mistreatment is difficult to quantify due to issues over definitions, differences in study methodology, and challenges in gathering and assessing sensitive information that is dependent on individual recall, interpretation, and willingness to report.1,25,8 Even medical trainees who are victims of serious physical sexual abuse are unlikely to report incidents to university authorities or the police.8,22 In a 2018 survey, over 80% of female staff in an academic medical center disclosed at least one incident of sexual harassment within the previous year, but only 10-20% of these individuals reported such incidents.11,12 Barriers to reporting included fear of not being believed, incidents being minimized or not taken seriously, and concerns about retaliation or being identified as a troublemaker.5,14

Gender-based discrimination and mistreatment take multiple forms.15 A National Academies of Sciences, Engineering, and Medicine (NASEM) report defined three categories: i.e., gender harassment (verbal and nonverbal behaviors that convey hostility, objectification, exclusion, or second-class status); unwanted sexual attention (verbal or physical unwelcome sexual advances, including unwanted touches or attempts to establish a sexual relationship despite discouragement, potentially including assault); and sexual coercion (favorable professional or educational treatment conditioned on compliance with sexual activity).7 Gender-based harassment accounts for the vast majority of incidents. All forms of gender-based mistreatment may cause serious and enduring harm to victims.7,15,19 Mistreatment of trainees and/or colleagues, especially if repeated and tolerated or ignored by the workplace culture, also impairs the learning environment and the functioning of professional teams.1,8,39

Reports indicate that previous generations of female medical students were subjected to more pervasive and severe mistreatment and were even less likely to report incidents.3,6,20-28 Prior to 1974, fewer than 10% of medical students were female (Table 1). Societal attitudes about appropriate female roles and behavior were different, and women entering a male-dominated profession anticipated a hostile environment.20-28 A 1973 survey described female medical students experiencing an unrelenting recital of bad things.25 Respondents to that survey reported pervasive mistreatment covering a complete spectrum from institutional policies and practices to interpersonal discrimination, harassment, and abuse.25 In a culture that endorsed bullying and mistreatment of all trainees as opportunities to demonstrate the dedication and stamina required of physicians, minority individuals faced extra pressure to prove themselves ‘tough enough for medicine.’25-28 Although much has changed and women are no longer numerically a minority group in medicine, the struggle to eliminate sexual harassment from academic medicine continues. Recommendations for effective programs stress the need to include all women regardless of role in the institution (students, faculty, staff, or other) and to ensure that diverse voices are heard.19,29,30 We believe that women who trained in the hostile environment of previous generations should also be heard. Their unique perspective provides historical context, and their insights as survivors could make useful contributions to ongoing efforts to eliminate mistreatment of women in the profession.
Table 1. Alumnae oral history study participants by class.

<table>
<thead>
<tr>
<th>Year</th>
<th>Participants</th>
<th>Female Graduates</th>
<th>Total Graduates</th>
<th>% Female Graduates (institution)</th>
<th>% Female Graduates (U.S.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1948</td>
<td>1</td>
<td>5</td>
<td>55</td>
<td>9.0%</td>
<td>7.1</td>
</tr>
<tr>
<td>1958</td>
<td>1</td>
<td>4</td>
<td>105</td>
<td>3.8%</td>
<td>5.1</td>
</tr>
<tr>
<td>1960</td>
<td>1</td>
<td>5</td>
<td>98</td>
<td>5.1%</td>
<td>5.7</td>
</tr>
<tr>
<td>1964</td>
<td>1</td>
<td>2</td>
<td>102</td>
<td>2.0%</td>
<td>6.1</td>
</tr>
<tr>
<td>1965</td>
<td>1</td>
<td>4</td>
<td>100</td>
<td>4.0%</td>
<td>7.3</td>
</tr>
<tr>
<td>1967</td>
<td>2</td>
<td>7</td>
<td>102</td>
<td>6.9%</td>
<td>7.5</td>
</tr>
<tr>
<td>1968</td>
<td>1</td>
<td>4</td>
<td>99</td>
<td>4.0%</td>
<td>8.0</td>
</tr>
<tr>
<td>1970</td>
<td>2</td>
<td>7</td>
<td>119</td>
<td>5.9%</td>
<td>8.4</td>
</tr>
<tr>
<td>1971</td>
<td>1</td>
<td>7</td>
<td>121</td>
<td>5.8%</td>
<td>9.2</td>
</tr>
<tr>
<td>1972</td>
<td>5</td>
<td>9</td>
<td>125</td>
<td>7.2%</td>
<td>9.0</td>
</tr>
<tr>
<td>1973</td>
<td>5</td>
<td>9</td>
<td>119</td>
<td>7.6%</td>
<td>9.1</td>
</tr>
<tr>
<td>1974</td>
<td>9</td>
<td>28</td>
<td>239</td>
<td>11.7%</td>
<td>11.1</td>
</tr>
<tr>
<td>1975</td>
<td>7</td>
<td>30</td>
<td>148</td>
<td>20.0%</td>
<td>13.4</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>121</td>
<td>1,532</td>
<td>14.3%</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

Note: 1974 had two graduating classes due to overlap of first class of experimental three-year curriculum introduced in 1971 with legacy class of previous four-year curriculum.

Sources for national data:

METHODS

This report utilizes data from an oral history project involving alumnae of the University of Kansas School of Medicine (KUSM) who graduated prior to 1975. The cutoff date was determined by the first year in which women represented more than 20% of graduates. We used announcements in alumni newsletters to recruit volunteers from the class of 1975 and earlier who were willing to share their experiences of life as a female physician. All volunteers who were able to participate were accepted into the study and participants provided written consent. During the winter of 2020-2021, we conducted structured interviews via Zoom, following the Oral History Association guidelines for data-gathering during the COVID-19 pandemic. The interview guide was developed based on literature review, experience with a previous project, and input from an advisory board consisting of graduates from the years included, current female faculty leaders, and representatives of the Medical Alumni Association. Members of the advisory board also assisted in recruitment of participants, development, and piloting of the interview guide, and provided formal member checking of study findings for validity.

All interviews were facilitated by a retired physician (AW) who is a longstanding faculty member at KUSM and 1971 graduate of another institution. Each interview lasted 45-120 minutes and covered the interviewee’s experience of life as a female physician in chronological order. Towards the end of the interview, we asked the interviewee’s opinion of the #MeToo movement, followed by questions about personal perceptions of sexual harassment and awareness of harassment of other women in medicine. The interviews were video recorded and transcribed. Each interviewee was given the opportunity to review the transcript of her interview and make any corrections, additions, clarifications, or deletions.

We assessed the recording and transcript of each interview using a thematic analysis approach, a method to identify and interpret patterns of meaning across qualitative data. Each investigator independently coded the narrative comments. We then established consensus on an agreed coding framework and identified patterns of commonality and divergent views. We next developed consensus on the names of the themes and identified illustrative quotations to defend each theme. The final qualitative analysis was completed by consensus among the three investigators. We resolved any differences in interpretation by discussion and joint review of the recorded sessions.

This report concerns the responses to the questions about #MeToo and sexual harassment as well as all information about gender-based mistreatment volunteered during the interviews. Other aspects of the oral histories will be reported at a later date. This study was approved by the University of Kansas Medical Center’s Institutional Review Board.

RESULTS

Nine volunteers could not be contacted or were unwilling or unable to complete interviews. All of the remaining 37 volunteers participated in the study. They were members of 13 graduating classes from 1948-1975. The total number of female graduates in each class ranged from 2 (2/102:2%) in 1964 to 30 (30/148:20%) in 1975. The 37 alumnae interviewed represented 31% of the 121 female graduates in the classes represented in the study (Table 1).

All interviewees described firsthand experiences consistent with the NASEM definition of gender harassment and reported knowing students who had been subject to the more serious forms of sexual abuse (Table 2). Twenty (54%) stated that gender harassment and unwanted sexual attention were experienced by all female students. When directly asked, three individuals denied experiencing any gender-based mistreatment personally, but each of these women had described both personal and observed incidents of gender harassment during her recollections of medical training. Twenty (54%) interviewees volunteered personal examples of unwanted sexual attention including being propositioned and/or inappropriate physical contact or abuse. Six of these women described situations in which they averted physically dangerous situations and one disclosed being sexually groomed and frequently assaulted by a faculty member. Three (8%) interviewees disclosed examples of sexual coercion. Nine (24%) women commented that they were targeted less than others because they were older, married, had children, perceived themselves as physically unattractive, or had difficult personalities.
## Table 2. Sexual harassment and related issues during medical school (N = 37).

<table>
<thead>
<tr>
<th>Issue</th>
<th>Number (%) Reporting</th>
<th>Illustrative Quotations</th>
</tr>
</thead>
</table>
| Gender harassment                     | All                  | • There was widespread sexual harassment by faculty, everyone was targeted.  
  • Was I sexually harassed? Yeah, all the time.  
  • Women do get harassed in medicine, constantly.  
  • There was this disbelief that women could be doctors. We were treated like it was a BIG favor to be in medical school. Women were treated SO differently from the guys. |
| Unwanted sexual attention             | 20 (54%)             | • Guys would constantly try to do stuff – being grabby, making comments, giving us all the wrong kind of attention. There was a lot of stuff, even from the married men. Men are intimidated by smart women, so they try to put you down, play on your insecurity. Say things like ‘you’re not a real woman’ if you didn’t go along with the sexist remarks and behaviors. It was everywhere, all the time.  
  • There was a departmental dinner where the women kept moving away from one man. When I ended up next to him, he was all handsy under the table.  
  • The male junior faculty were a problem. One of the instructors in anatomy brushed his hand on girls’ bottoms every single time he walked past. Nobody ever called him out for it.  
  • One of the professors was well known for wanting to have an affair with every single female going through. Nearly everyone was approached. I escaped by the skin of my teeth as I had visitors when he came to my apartment. He was never called out publicly.  
  • A hospital staff physician would find out when women were working in the Emergency Department and come in late at night to harass them. There was some physical contact. I know of three women involved – could have been more. A forceful head nurse observed an incident and put a stop to the practice. |
| Sexual coercion                        | 3 (8%)               | • There were multiple things like a professor wanting to date or getting a good letter from the assistant dean if I met him at a bar. That never sounded like a date — more like a proposition. It is just the way it was. |

### Definitions

- **Gender harassment**: Verbal and nonverbal behaviors that convey hostility, objectification, exclusion, or second-class status.
- **Unwanted sexual attention**: Verbal or physical unwelcome sexual advances, including unwanted touches or attempts to establish a sexual relationship despite discouragement, potentially including assault.
- **Sexual coercion**: Offers of favorable professional or educational treatment conditioned on compliance with sexual activity.
Male faculty members were the most frequently identified perpetrators, followed by residents and fellow students. None of the interviewees reported incidents to medical school or other authorities. To cope with sexual harassment, individuals used verbal responses or removed themselves from situations if possible. Most described tolerating mistreatment as a perceived requirement of completing medical education.

Opinions of “#MeToo” (Table 3). Twenty-eight (76%) interviewees had positive opinions of the #MeToo movement. The degree of endorsement ranged from robust, enthusiastic support to more qualified approval. Four (11%) interviewees had negative opinions. These varied from outright dismissal of the movement to considering it outdated and unnecessary. These women believed that their roles as physicians were more important than any personal concerns about discrimination or harassment and that a woman aspiring to be a physician should be able to deal with any challenging situation. The remaining five (13.5%) interviewees were ambivalent or unwilling to comment on the topic.

Seventeen (46%) interviewees, including many who supported the #MeToo movement, expressed concern that the movement and similar initiatives could inhibit communication and damage working relationships in healthcare teams. Twelve (32%) interviewees believed the movement had gone too far and eight (22%) were concerned about false or unsupported accusations.

DISCUSSION

These first-hand accounts verify that during the three decades (1944 to 1975), female medical students experienced pervasive gender-based mistreatment ranging from inappropriate verbal comments and discrimination in daily activities to less common sexual coercion and even assault. Many interviewees stressed that such treatment of women was “normal” at the time, and that medical training was also abusive to male trainees. As women and members of a minority group, they expected to be in “double jeopardy” of abuse, justified as necessary to stringently test their physical and emotional stamina. They did not expect nor seek intervention from authorities to address inappropriate behavior, no matter how severe. Conversely, they were reluctant to do anything that might draw attention to themselves or have negative repercussions. We were surprised by the lack of group action to improve their situation, even during the turbulent period of student protests in the early 1970s. The only report of push back concerned use of pornographic material in lectures. This mild protest was quickly squashed (Table 2). Each woman navigated each situation to the best of her ability, reminiscent of a quote from a 1950s student at another institution, “We believed the quieter we were, the more likely we were to graduate.”

Overall, mistreatment was expected, minimized, and endured by female students, partly because it was perceived as normal for the time and environment, and partly as a challenge to prove themselves worthy of becoming physicians. The norms of the time might explain why the women did not perceive themselves as exposed to gender-based mistreatment when directly asked, despite volunteering examples of discrimination and sexual harassment during their interviews. Our participants described personal examples of utilizing all of the principal coping mechanisms for abuse described in the literature such as avoidance, minimizing, and self-blame.

Several interviewees commented that their experiences seemed normal at the time and should not be judged by current values. Despite many distressing, unfair, and even dangerous experiences, almost all interviewees looked back on their time as an exciting, challenging, and rewarding period of personal growth rather than the unrelentingly misogynistic experience portrayed in some of the contemporary literature. Only two interviewees expressed enduring bitterness about their treatment; the majority conveyed pride in their resilience and ability to overcome mistreatment to develop successful careers.

Pride in their endurance and resilience may explain the mixed support of #MeToo and similar movements. The majority of interviewees supported the movement, some expressing robust, highly enthusiastic comments. Nevertheless, many voiced concerns about over-reach or negative consequences, and a few were unsupportive or even hostile. The major theme of the concerns and negative comments was that women aspiring to be physicians should expect, even embrace, a rigorous training environment and be able to avoid and, or manage adversity, including gender-based mistreatment. A related theme was that the work of a physician was of paramount importance, that the duty and privilege of caring for patients superseded any personal distress, disrespect, or abuse experienced by the physician.

In a large national survey conducted by the Pew Research Center in 2022, 49% of women over 65 years of age supported the #MeToo movement. These national survey data suggest that our interviewees were more supportive of #MeToo than other U.S. women, but also more concerned about the movement going too far and generating adverse outcomes through unfounded accusations and/or damage to work environments. We have been unable to find data on the opinions of current female physicians or trainees on #MeToo. Such information would provide interesting comparisons for our findings. More importantly, the data would be useful in designing, implementing, and monitoring the effectiveness of programs to address gender-based mistreatment during medical training.

Our findings should be interpreted with caution due to the many limitations of oral histories concerning events that took place at least four decades earlier, as well as potential volunteer bias and an unbalanced report of gender-based mistreatment. Our interviewees were a self-selected group of alumnae who could be contacted, were willing to participate, and were able to complete interviews using teleconferencing systems. Narratives could have been distorted by selective recall, reinterpretation of events, unwillingness to disclose sensitive or distressing information, or other factors. We were also reminded by several interviewees that much behavior now regarded as inappropriate, was accepted as normal at the time and that they only recognized some experiences as harassment in retrospect. Much of the routine discrimination toward women as an unwelcome minority or second-class citizens during medical training was not recalled or thought worthy of mention. Our findings are limited to graduates of a single institution and only one interviewee identified as non-White. We are also aware

Table 3. Alumnae perspectives on the "#Me Too" movement (N = 37).

<table>
<thead>
<tr>
<th>Theme</th>
<th>Number (%) Reporting</th>
<th>Illustrative Quotations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive/supportive</td>
<td>28 (76%)</td>
<td>• I think its high time. We have overlooked so much. We tolerated things. It’s great, liberating for women.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It’s always been there but now coming to the surface. The men are being called on it. We just didn’t talk about it. Men got away with things, perhaps connected to their jobs. Now it is taken seriously and there are consequences for men.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It’s high time, long overdue.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• I’m all for it. These things have to be brought into public light. When we sweep things under the rug, it leads to problems.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Absolutely necessary to bring things to the surface.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It's been so long in coming. It’s appropriate, needs to be out there.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It’s good. Women have been oppressed for a long time in ways that are not obvious.</td>
</tr>
<tr>
<td>Not aware/unsure</td>
<td>5 (13.5%)</td>
<td>• I don’t know what to say.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• I’m not sure what that is. Don’t have anything to say about it.</td>
</tr>
<tr>
<td>Not supportive</td>
<td>4 (11%)</td>
<td>• I knew one woman who sued claiming she was not treated with respect, but I never agreed with any of it.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• I don’t think about it. I have more important things to do. Women’s lib turns me off.</td>
</tr>
<tr>
<td>Concerns about over-reach</td>
<td>12 (32%)</td>
<td>• #Me Too is for the most part good- sometimes goes too far.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Maybe some going overboard.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Women are so touchy now. I see dying patients every day and work with anxious patients, people- and women are worried if a guy touches a shoulder, they fuss and shudder!</td>
</tr>
<tr>
<td>Concerns about false or unsupported accusations</td>
<td>8 (22%)</td>
<td>• Don’t know how much to believe. Is it legitimate, especially if it happened like 15 years age? Who can remember what exactly happened?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• A lot of bad stuff went on, but the innocent could be wrongly accused. Reminds me of the recovered memory of abuse situations a few years ago.</td>
</tr>
<tr>
<td>Concerns about damage to collegial relationships</td>
<td>17 (46%)</td>
<td>• There are gradations, not everyone is Harvey Weinstein, not everyone is that obvious. Now my son is so concerned in business that he will not interview or meet with any woman alone unless someone else is present - can’t even have lunch with someone anymore.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• I hope it doesn’t go too far and the men are “walking on eggshells”.</td>
</tr>
</tbody>
</table>

of the inherent risk of interviewer and evaluator bias despite designing the study to minimize the potential for our individual experiences and perspectives to influence our findings.

Nevertheless, these insights and first-hand accounts provide valuable reminders of how much has changed in the experience of women in medicine within the lifetimes of senior female physicians. While much remains to be done to achieve a culture of genuine diversity and inclusion for all individuals, current female students do not learn in the environment of overt, accepted, and pervasive mistreatment described by our interviewees or believe that surviving misogynistic abuse is required to prove oneself tough enough to be a physician.

Given their experiences of sexual harassment and abuse, we were surprised by the misgivings about #MeToo expressed by a substantial minority of interviewees and the antipathy of a small group. This may reflect the experience of generations who lived through attempts to force societal change through violent protests in the 1960s and 1970s and had learned to temper passion with prudence and patience to achieve their goals. The women who entered medicine in the three decades following the Second World War faced multiple challenges. They did not lack courage or determination, but their narratives conveyed that, like many women of their generation, they learned to navigate obstacles and avoid hostile situations rather than confront mistreatment.20-24,27,34-35 They had no expectation of institutional intervention to improve the treatment of women and could do little to change the prevailing culture except by gaining the respect of male faculty, classmates, and others through their work and social interactions. They relied on intelligence, hard work, endurance, and often humor to succeed as physicians.

Importantly, our interviewees had no wish to leave a legacy of bitterness or regret. They opposed any use of their experiences to generate indignation or claim retribution for the previous mistreatment of women in the profession. Rather, they emphasized that women continue to face different challenges as medicine evolves and that the experiences of previous generations may be of limited relevance to current and future physicians. Nevertheless, the experiences of women who were an oppressed minority in the profession can inform efforts toward diversity and inclusion for all. This generation lived through profound changes in the numbers and status of women in medicine. They have been variously described as the landing party of an invading force intent on establishing a beachhead in the profession and holding on,36 or as intrepid pioneers, seeking to settle new lands and change existing cultures. While both military and colonizing metaphors are
limited (and potentially inappropriate or offensive), the achievements and contributions of this transitional generation of women should be more widely recognized. Many of the positive changes in the profession, not just those regarding the status of women, result from their dedication, resilience, tenacity, and years of service to medicine.

CONCLUSIONS

Women who trained in medicine prior to 1975 experienced pervasive gender-based mistreatment, ranging from verbal harassment to sexual coercion and assault. While generally supportive of #MeToo, many had concerns about over-reach and potential adverse consequences, and few were ambivalent or opposed to the movement.

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Keywords: gender bias, medical education, women’s rights, sexual harassment, anthropology cultural
Impact of JayDoc Free Clinic on Emergency Department Usage in Kansas City

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ABSTRACT

Introduction. JayDoc Free Clinic (JayDoc) serves medical needs of uninsured patients in the Kansas City metropolitan area. It is known that patients who have access to primary care are less likely to visit their local Emergency Department (ED) for non-emergent needs. However, it is not well described if JayDoc lowers usage of the University of Kansas Health System (TUKHS) ED. This is the first study to assess the patient referral process between TUKHS ED and JayDoc.

Methods. The authors administered a voluntary survey to every patient triaged at JayDoc, even if they were ultimately not accepted for a visit. Items on the questionnaire included health insurance status, primary language, and access to a primary care physician. The authors included questions on the usage of TUKHS ED in the last 12 months.

Results. Seventy-three patients completed the questionnaire. Approximately 10% of respondents reported they visited the ED in the last 12 months and received a referral to JayDoc from staff. However, authors observed no statistically significant difference in the proportion of new patients who used the ED in the last 12 months compared to that of returning patients.

Conclusions. Results of this study demonstrated an existing referral system between JayDoc and TUKHS ED. However, the authors could not conclude that JayDoc reduces non-emergent ED visits among its patient population. Future initiatives will include further education to ED providers to increase the number of patients being referred to JayDoc.


INTRODUCTION

Use of the ED for non-emergent needs negatively affects patients, physicians, and hospital systems across the United States. Prior studies have defined ED visits as “avoidable” if they “did not require any diagnostic or screening services, procedures or medications, and were discharged home.” Uninsured individuals are more likely to visit the ED for non-emergent ailments. The non-emergent use of EDs is considered financially unsustainable for patients and those who utilize EDs as a replacement for primary care can suffer from unnecessary testing and a lack of care coordination. In addition to insurance status, proximity to alternative healthcare options affects ED utilization. There have been observed correlations between decreased use of the ED for low acuity illnesses and presence of an urgent care clinic within one mile of patient residence. This illustrates that the barriers to accessing alternative healthcare options, such as distance or insurance status, results in increased rates of ED use.

Safety net clinics and student-run free clinics (SRFC) often serve as healthcare alternatives to EDs for acute conditions. These clinics provide services to those lacking insurance or access to primary care. The patient population served by these clinics largely overlaps with the group of patients more likely to use the ED for non-emergent illnesses. A study conducted at a SRFC in Boston, Massachusetts observed a decreased rate of ED utilization among patients who established care at the SRFC. The results from this study provide insight on how to reduce the care burden for patients served by SRFCs. JayDoc in Kansas City, KS has tried to decrease the burden posed by non-emergent ED use by providing ED staff at TUKHS with materials outlining clinic resources. These materials are to be distributed to uninsured patients upon discharge from the ED.

There has not been a prior assessment of the efficacy of the educational materials provided to TUKHS staff and whether they successfully refer patients to JayDoc. Reviewing the efficacy of this program would allow leadership at JayDoc to understand if the services provided by the clinic are reducing non-emergent ED visits and implement necessary changes to our educational programs. This observational study investigates if previously established JayDoc patients are less likely to utilize the ED when compared to patients who are new to the clinic. This study also assesses the method in which patients are referred to JayDoc, either via the ED or another source.

METHODS

JayDoc operates an acute care clinic on a triage basis every Monday and Wednesday. The triage process determines if a patient’s chief complaint is within our scope of care and decides how many patients can be seen on a given night. We chose to utilize the triage process instead of the patient visit to avoid excluding patients who did not meet criteria to be seen in clinic that night. A qualitative cross-sectional survey was administered at JayDoc over a three-month span from December 1, 2021, to March 14, 2022. Any patient over the age of 18 years who completed the triage process met eligibility requirements for the study.

Once the standard triage survey was complete, the volunteer conducting triage explained the study to the patient and obtained informed consent from those interested in participating. Survey questions included demographic information, insurance status, current chief complaint, and ED utilization the prior year. No patient identifiers such as name, date of birth, medical record number, or home address were collected. We obtained Institutional Review Board approval from The University of Kansas before survey responses were collected. To investigate the probability of other acute care services, we collected data on the number of urgent care services and ED per zip code using Google Maps.

Our primary outcome was whether a patient had visited TUKHS ED in the last 12 months. Secondary outcomes included if the patient had received a referral to JayDoc and the method in which the patient received the referral. Due to the cross-sectional nature of our study, a Chi-Squared test and risk ratio were calculated to assess the relationship between exposure to care at JayDoc and ED utilization in the last 12 months. If the patient indicated on the survey that they received prior care at JayDoc for any reason, they were considered exposed.

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RESULTS

During the dates the survey was administered, 250 patients were triaged in clinic. Of those, 73 (29.2%) patients agreed to be surveyed about their ED utilization following the survey format shown (Appendix; available online at journals.ku.edu/kjm). Of the 73 patients, 71 (97%) met criteria to be seen at JayDoc for their chief complaint. Table 1 summarizes the primary languages, insurance status, primary care access, and JayDoc visit history of the participants.

Table 1. Patient demographics (N = 73).

<table>
<thead>
<tr>
<th>Primary Language</th>
<th>Insurance Status</th>
<th>Primary Care Provider</th>
<th>Seen at JayDoc Before</th>
</tr>
</thead>
<tbody>
<tr>
<td>English (%)</td>
<td>Spanish (%)</td>
<td>Other (%)</td>
<td>Insured (%)</td>
</tr>
<tr>
<td>41 (56.2)</td>
<td>26 (35.6)</td>
<td>6 (8.2)</td>
<td>12 (16.4)</td>
</tr>
</tbody>
</table>

While the survey participants lived in 33 different zip codes in the Kansas City metropolitan area, six zip codes accounted for 47.6% of participant residences (Table 2). One of these zip codes encompassed both TUKHS ED and JayDoc. Of note, the remaining five zip codes contained zero EDs and varied in their number of urgent care clinics. Zip code distance from JayDoc was measured from the geographic center of the zip code to the clinic’s address.

Table 2. Incidence of urgent care clinics and emergency departments by zip code.

<table>
<thead>
<tr>
<th>Zip Code</th>
<th>Distance from JayDoc (Miles)</th>
<th>Number of EDs</th>
<th>Number of Urgent Care Clinics</th>
</tr>
</thead>
<tbody>
<tr>
<td>66101</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>66102</td>
<td>6.7</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>66103</td>
<td>1.4</td>
<td>1*</td>
<td>1**</td>
</tr>
<tr>
<td>66104</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>66106</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>64055</td>
<td>15</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

*TUKHS Emergency Department  **JayDoc Free Clinic

A total of 16 (22%) patients who completed the survey reported they visited TUKHS ED in the last 12 months. It was later identified that two previously established JayDoc patients incorrectly answered “yes” to TUKHS ED use, and had visited a different ED. These patient responses were changed to “no” for analysis. There was no difference (p=0.05) in ED utilization between new and returning JayDoc patients. The χ² test of independence reported χ² = 0.04, indicating no statistically significant difference in ED usage between new patients and returning patients in the last 12 months (p=0.84). The risk ratio between these two groups was calculated using a 95% confidence level and equaled 0.91 [0.35, 2.88]. This illustrated that there was not an increased risk in visiting the ED based on prior establishment of care at JayDoc.

Of the 14 patients who visited TUKHS ED in the last 12 months, 12 (86%) visited JayDoc for the same chief complaint. Seven (58%) of those patients reported being referred by ED staff, three (25%) reported being referred by a family member or friend, one (8%) patient learned about JayDoc through a Facebook advertisement, and one (8%) patient did not specify their referral source (Figure 1).

DISCUSSION

Only 50% of patients who visited TUKHS ED in the last 12 months received a referral to JayDoc, indicating missed opportunities to educate patients on free healthcare resources. This study informed JayDoc leadership on the gaps in patient education that could prevent non-emergent ED usage among individuals who have previously used clinic services. Future endeavors should center around identifying avenues to close these education gaps. In the ED, this could take the form of automatically adding information on clinic services to the discharge summary of any patient without a primary care provider (PCP) or insurance listed in their electronic medical record. In clinic, this could involve sending every new patient home with information on which ailments JayDoc can treat, which ailments can be treated by other safety net clinics in the area, and which ailments require a visit to the ED. Additional points for education can include lists of acute care services in proximity to patient residence, resources for low cost or free transportation, and a complete schedule of operating hours for acute care services in the region. There are current programs offered by JayDoc to enroll eligible patients in Medicaid and connect patients to PCPs. Future studies could explore if participation in either of these programs affect non-emergent use of the ED.

This observational cross-sectional study sought to determine if an existing referral program between an ED and a SRFC prevented patients established with that clinic from utilizing the ED. We did not observe a statistically significant difference in the rate of ED utilization between patients previously seen in clinic compared to new patients. We also observed that several patients seen in the ED were not given appropriate clinic education materials, identifying a shortcoming in our referral system. Other SRFCs can use the results and associated discussion of this study to guide how they educate patients on appropriate resources and create their own partnerships with EDs in their community.
REFERENCES


Keywords: emergency department, acute care services, insurance, primary care, referral
INTRODUCTION

Human Parechovirus (HPeV) is a single-stranded RNA virus belonging to the *Picornaviridae* family. Despite being initially classified as echovirus 22 and 23 among human enteroviruses due to clinical and morphological characteristics, further research has revealed that HPeV possesses unique genome organization, structure, and replication mechanisms that differentiate it from other picornavirus groups.1 There are currently 17 known subtypes of HPeV, types 1 and 3 being the most prevalent and type 3 associated with more severe diseases.2-4 HPeV is known to cause respiratory and gastrointestinal illnesses. HPeV infection can be of varying illness severity, ranging from asymptomatic to severe disease including sepsis, meningitis, and in rare cases, encephalitis.2 While most symptomatic HPeV infections are in children younger than two years, the more severe cases are often associated with neonates or infants less than three months of age.3 A study done in Australia showed that cerebrospinal fluid (CSF) pleocytosis was absent in 96% of cases, making the diagnosis more challenging.6 Treatment is mostly supportive care with some reported benefits of intravenous immunoglobulin (IVIg) and corticosteroid as there are no standardized treatment modalities.7-9

HPeV type 3 (HPeV3), the dominant genotype responsible for most severe cases, typically follows a biennial pattern, showing higher activity in even-numbered years.10 In July 2022, the Centers for Disease Control and Prevention (CDC) issued a health advisory after receiving reports of neonates and infants with HPeV illness.11 In this report, we describe four neonates admitted for severe HPeV illness in the summer of 2022 successfully treated with IVIg and corticosteroids.

CASE REPORT

Case 1

A six-day-old previously healthy female born at 40 weeks gestational age (GA) presented to the hospital with a temperature of 100.3°F (37.9°C), decreased responsiveness, poor latch while breastfeeding, and high-pitched crying. On hospital day two, the patient developed hypopnea associated with lateral eye deviation that was refractory to lorazepam, necessitating transfer from the pediatric intensive care unit (PICU). The patient underwent emergent endotracheal intubation and was started on intravenous (IV) levetiracetam and phenobarbital. Seizures initially improved per continuous video electroencephalogram (cEEG), but ultimately required IV midazolam for sustained control. Full sepsis evaluation including blood, urine, and CSF studies was completed. Spinal fluid analysis demonstrated a white blood cell count of 6 cells/microL, an elevated protein of 96 mg/dL, and polymerase chain reaction (PCR) pathogen testing was positive for HPeV (Table 1). Empiric antibiotics were stopped and supportive management, including antiepileptics, was continued.

On hospital day three, the patient demonstrated symptoms of shock from the ongoing inflammatory response requiring norepinephrine, epinephrine, and hydrocortisone. On hospital day four, the patient developed intermittent subclinical seizures in the left central region despite antiepileptics. IV pentobarbital infusion was initiated to achieve burst suppression on EEG. IVIg was administered due to the ongoing hyperinflammatory state and subclinical seizures. Magnetic resonance imaging (MRI) of the brain was obtained after 24 hours of burst suppression on cEEG and showed extensive diffusion restriction involving the supratentorial juxtacortical and periventricular white matter, bilateral thalami, and corpus callosum with associated diffuse meningeal enhancement consistent with parechovirus meningoencephalitis (Figure 1).

By hospital day seven, the patient was successfully weaned from pentobarbital and continued levetiracetam and phenobarbital. She was extubated on hospital day 10 and transferred back to the pediatrics floor for continued monitoring and rehabilitation. By hospital day 17, she progressed to enteric feeds via nasogastric (NG) tube and was considered stable for discharge with close outpatient follow-up.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission month, year</td>
<td>June 2022</td>
<td>July 2022</td>
<td>June 2022</td>
<td>August 2022</td>
</tr>
<tr>
<td>Location</td>
<td>Kansas</td>
<td>Kansas</td>
<td>West Virginia</td>
<td>West Virginia</td>
</tr>
<tr>
<td>Age, days</td>
<td>6</td>
<td>42</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>40</td>
<td>34</td>
<td>36.6</td>
<td>37</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Admission weight, kg</td>
<td>3.9</td>
<td>3.82</td>
<td>2.86</td>
<td>2.7</td>
</tr>
<tr>
<td>PRISM 3</td>
<td>10</td>
<td>15</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Fever, poor feeding</td>
<td>Hypothermia, poor feeding</td>
<td>Hypothermia, poor feeding, apnea, decreased tone</td>
<td>Hypothermia, poor feeding, apnea, decreased tone, erythroderma</td>
</tr>
<tr>
<td>Cerebrospinal Fluid analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC, cells/µL</td>
<td>6</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Protein, g/dL</td>
<td>96</td>
<td>112</td>
<td>71</td>
<td>98</td>
</tr>
<tr>
<td>Glucose, g/dL</td>
<td>63</td>
<td>44</td>
<td>61</td>
<td>79</td>
</tr>
<tr>
<td>HPeV PCR</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Complete blood count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC, x10^3/µL</td>
<td>6.3</td>
<td>7.6</td>
<td>8.84</td>
<td>5.32</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>15.0</td>
<td>11.0</td>
<td>16.2</td>
<td>14.6</td>
</tr>
<tr>
<td>Platelets, x10^3/µL</td>
<td>213</td>
<td>266</td>
<td>248</td>
<td>176</td>
</tr>
<tr>
<td>Lymphocytes %</td>
<td>8.4</td>
<td>26.7</td>
<td>13.4</td>
<td>17.2</td>
</tr>
<tr>
<td>Neutrophils %</td>
<td>82.6</td>
<td>50.2</td>
<td>66.0</td>
<td>62.5</td>
</tr>
<tr>
<td>Monocytes %</td>
<td>7.8</td>
<td>21.3</td>
<td>17.5</td>
<td>13.5</td>
</tr>
<tr>
<td>Eosinophils %</td>
<td>0.2</td>
<td>0.1</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>PICU admission, hospital day</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Electrographic seizures</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Asymmetric slowing</td>
</tr>
<tr>
<td>Antiepileptic medications</td>
<td>Lorazepam, Phenobarbital, Levetiracetam, Midazolam infusion, Pentobarbital infusion</td>
<td>Phenobarbital, Levetiracetam, Pentobarbital infusion</td>
<td>Clobazam, Fosphenytoin Levetiracetam Midazolam Oxcarbazepine, Topiramate, Pentobarbital infusion</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Discharge antiepileptic medications</td>
<td>Phenobarbital Levetiracetam</td>
<td>Phenobarbital Levetiracetam</td>
<td>Levetiracetam Oxcarbazepine topiramate</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>MRI brain findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>Extensive diffusion restriction involving the bilateral supratentorial juxtacortical and periventricular white matter bilateral thalami and corpus callosum</td>
<td>Extensive abnormal diffusion restriction involving the periventricular and subcortical white matter as well as the corpus callosum and internal capsule patchy involvement of the bilateral thalami</td>
<td>Restricted diffusion within the white matter of bilateral cerebral hemispheres, the internal and external capsules, the corpus callosum, and thalami</td>
<td>Small foci of restricted diffusion noted within the bilateral periventricular white matter with associated mild increased signal on FLAIR imaging within the periventricular white matter</td>
</tr>
<tr>
<td>Vasoactives infusions</td>
<td>Epinephrine, Norepinephrine Not obtained</td>
<td>Epinephrine, Norepinephrine, Vasopressin 768</td>
<td>Epinephrine, Norepinephrine Not obtained</td>
<td>Epinephrine, Norepinephrine Not obtained</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>Not obtained</td>
<td>Not obtained</td>
<td>Not obtained</td>
<td>Not obtained</td>
</tr>
<tr>
<td>pNT-BNP peak (pg/ml)</td>
<td>Not obtained</td>
<td>Not obtained</td>
<td>Not obtained</td>
<td>43,502</td>
</tr>
<tr>
<td>Troponin (pg/ml)</td>
<td>Not obtained</td>
<td>Not obtained</td>
<td>913</td>
<td>661</td>
</tr>
</tbody>
</table>
Table 1. Demographics, presenting symptoms, and results of cerebrospinal fluid analysis. continued.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous Immunoglobulin (IVIg) dose</td>
<td>IVIG 1g/kg Hydrocortisone 1 mg/kg every six hours</td>
<td>IVIG 1g/kg Hydrocortisone 1 mg/kg every six hours</td>
<td>IVIG 1g/kg Methylprednisolone 30 mg/kg/d</td>
<td>IVIG 1g/kg Methylprednisolone 30 mg/kg/d</td>
</tr>
<tr>
<td>Steroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator days</td>
<td>9</td>
<td>7</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>PICU LOS, days</td>
<td>11</td>
<td>11</td>
<td>46</td>
<td>17</td>
</tr>
<tr>
<td>Hospital LOS, days</td>
<td>17</td>
<td>11</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Functional State Scale</td>
<td>15/30</td>
<td>13/30</td>
<td>15/30</td>
<td>10/30</td>
</tr>
<tr>
<td>Long-term neurodevelopmental outcomes</td>
<td>Moderate developmental delay On Phenobarbital for seizures Diffuse hypotonia</td>
<td>Mild developmental delays No spasticity</td>
<td>Significant motor developmental delay</td>
<td>Normal development</td>
</tr>
</tbody>
</table>

Case 2
A six-week-old male born at 34 weeks GA presented to the hospital with fussiness, hypothermia, poor feeding, and episodes of stiffening at home. A full sepsis workup was done in the emergency department including a spinal fluid analysis with elevated WBC of 10 cells/μL, elevated protein 112 mg/dL, and positive HPeV on PCR panel (Table 1). Troponin I and brain natriuretic peptide (BNP) were significantly elevated, indicating signs of myocarditis (Table 1). Non-contrast computed tomography (CT) head demonstrated multiple areas of supratentorial poor gray-white matter differentiation concerning for cerebral edema (Figure 2). The patient required endotracheal intubation secondary to apnea-associated status epilepticus. cEEG revealed frequent focal sharp wave discharges from both central and temporal regions. The patient was started on IV phenobarbital and levetiracetam. In the setting of profound hemodynamic instability and shock, the patient required norepinephrine, epinephrine, and vasopressin infusions in addition to intravenous hydrocortisone. IVIg treatment was administered over 10 hours.

Figure 2. MRI brain of patient 2 showing extensive abnormal diffusion restriction involving the periventricular and subcortical white matter as well as the corpus callosum and internal capsule patchy involvement of the bilateral thalami.

On hospital day two, there was evidence of refractory status epilepticus. The patient was started on continuous pentobarbital infusion. CSF cultures remained negative at 48 hours, and antibiotics were discontinued. Vasopressors and pentobarbital were gradually weaned by hospital day six. MRI brain with contrast showed extensive abnormal diffusion restriction involving the periventricular and subcortical white matter, the corpus callosum, the internal capsule, and patchy involvement of the bilateral thalami (Figure 2). The patient was extubated on hospital day 7 and discharged on hospital day 11 with close outpatient follow-up.

Case 3
A previously healthy 18-day-old male born at 36.6 weeks GA was admitted for a one-day history of poor feeding, irritability, and high-pitched crying. Twelve hours after admission, the patient developed lethargy, hypothermia (95.5°F [35.3°C]), and irregular respirations with resultant respiratory acidosis requiring transfer from the pediatrics floor to the PICU. The patient was placed on bilevel-positive airway pressure (BiPAP) with an initial improvement in respiratory acidosis. A full sepsis workup was completed, and spinal fluid analysis showed no pleocytosis with normal protein and glucose, but a CSF PCR panel was positive for HPeV. On hospital day three, the patient required significant fluid resuscitation for hemodynamic instability and was intubated due to recurrent apnea. His clinical status worsened with shock and disseminated intravascular coagulation (DIC; Table 1). A transthoracic echocardiogram (TTE) revealed normal cardiac function.

cEEG showed frequent interictal subclinical seizure activity reflecting status epilepticus with seizure focus on the left frontal-temporal-central region. Seizure management included intravenous levetiracetam and then phenobarbital to achieve seizure control. A single dose of IVIg was given on hospital day four, and his EEG continued to have focal abnormalities in the left frontal-temporal-central region. pBNP levels continued to rise dramatically to over 160,000 pg/ml by day seven. A repeat TTE was obtained and was notable for mild LV dilation with low-normal left ventricular systolic function, ejection fraction of 50% suggestive of possible viral myocarditis. Given TTE findings and persistently elevated pBNP, IVIg was restarted on hospital day seven, completing a five-day course. Repeat MRI and magnetic resonance
venography (MRV) brain with contrast was notable for severely restricted diffusion in the white matter of bilateral cerebral hemispheres, the internal and external capsules, the corpus callosum, and thalami, as well as a few areas of punctate hemorrhage. On hospital day 10, cEEG demonstrated worsening bilateral epileptiform activity, and pentobarbital infusion was started to achieve burst suppression. Intravenous methylprednisolone 30 mg/kg/day burst for three days followed by a taper was also initiated. His pBNP trended down rapidly thereafter and he was weaned off pentobarbital on hospital day 18 and was seizure free on intermittent antiepileptics.

A repeat MRI brain on hospital day 22 revealed severe, widespread leukomalacia. However, the patient remained seizure-free. He was successfully extubated on hospital day 33. Ultimately, he was discharged home on hospital day 55 on levetiracetam, oxcarbazepine, and topiramate. His neurological examination at that time was non-focal.

**Case 4**

A previously healthy seven-day-old female born at 37 weeks GA was admitted to the PICU for hypothermia (94°F [34.4°C]), hypotonia, and apnea requiring endotracheal intubation. Sepsis workup including lumbar puncture was not pursued on admission given unstable hemodynamics and coagulopathy, but empiric antimicrobials were initiated. On hospital day two, high-dose epinephrine and norepinephrine infusion were started for ongoing hemodynamic instability. Hematologic parameters revealed DIC, and the patient received vitamin K and FFP (Table 1). pBNP (16,649 pg/ml) and troponin (661 pg/ml) were elevated, although TTE showed normal cardiac function. On hospital day four, spinal fluid analysis showed no CSF pleocytosis, but the PCR was positive for HPeV. IVIg was initiated and continued for five days. EEG normalized as starting levetiracetam.

On hospital day six, she was weaned off vasopressors, and MRI/MRV brain with contrast was obtained revealing small foci of restricted diffusion within the bilateral periventricular white matter. On hospital day seven, she had a recurrence of asymmetric, but non-epileptiform, EEG changes with an abrupt rise in pBNP and hypofibrinogenemia despite declining troponin and inflammatory markers. Given the recurrence of lateralized EEG findings correlating with known ischemia on MRI, rising pBNP, and decreasing fibrinogen, a high-dose methylprednisolone 30 mg/kg/d was started. EEG normalized on day nine. She was extubated on hospital day 14, transferred to the pediatric floor, and was able to be discharged home by hospital day 17 on levetiracetam with no focal neurological deficits.

**DISCUSSION**

HPeV encompasses a wide clinical spectrum with more severe presentations being noted across the U.S. in 2022.10 We describe four neonates with severe HPeV illness presenting with seizures, sepsis, and multiorgan failure (Table 1). Studies have demonstrated that HPeV3 can cause severe sepsis-like illness, with fever, reduced feeding, neurological symptoms (such as irritability and seizures), and rash being the most frequent clinical signs observed in hospitalized children.12-15 According to a case series by Ristagno et al.,16 an early diagnosis can lead to a shorter duration of hospitalization, attenuated antibiotic use, and avoidance of unnecessary diagnostic tests in critically ill infants. Therefore, timely diagnosis and intervention can provide useful prognostic guidance for families, including favorable neurologic outcomes despite illness severity.10 While leukopenia accompanied by fever has been suggested as a distinctive characteristic of HPeV infection, there are no clinical features that can accurately differentiate HPeV3 infection from other viral or bacterial causes of sepsis in young infants. Therefore, it is necessary to have a low threshold for conducting blood and CSF testing for HPeV in acutely ill infants younger than six months. Prior research also indicates that HPeV meningoencephalitis frequently lacks CSF pleocytosis,17,18 so an elevated white blood cell count in CSF should not be used as a criterion to determine whether HPeV testing is required. CSF analysis is necessary to confirm the diagnosis, and molecular testing such as real-time (RT)-PCR is the most sensitive and specific method for detecting HPeV in CSF.19 Delayed diagnosis and treatment can result in severe complications, including encephalitis, hydrocephalus, and death.19

Unlike other forms of encephalitis and regardless of imaging results, HPeV can cause hypertension and bradycardia suggestive of possible cerebral edema.16 HPeV3 encephalitis typically affects only the white matter. MRI imaging characteristically shows focal frontal-predominant subcortical white matter and callosal involvement with excessive high signal intensity on diffusion weight imaging. Contrastingly, neonatal HSV encephalitis typically exhibits diffuse gray and white matter changes.20 According to a study by Midgley et al.,20 HPeV3 can cause severe neurologic illness in neonates and, in some cases can be associated with white matter changes. They found that severe HPeV3 infections requiring critical care management were more commonly seen in infants younger than three weeks and with older infants being less critical.20

Focal seizures as shown by our patients are like those seen in herpes simplex virus (HSV) encephalitis. In children, a focal seizure in a specific area of the brain suggests HSV encephalitis, but in neonates, other symptoms such as generalized seizure, lethargy, and irritability may also be present.2 In children, HSV encephalitis is commonly seen during the second or third week of life, whereas severe HPeV-A3-related disease is usually found in newborns and infants under four months of age.2

Currently, there are no antivirals or vaccinations for HPeV.21 The current mainstay of treatment of neonatal enterovirus infections, including HPeV, is supportive care. Potential treatment options for HPeV infection comprise IVIg substances that inhibit the capsid, and inhibitors targeting the 3C protease.18 The use of IVIg in treating severe diseases has been reported to have some favorable outcomes, like its use in treating severe enterovirus infections in neonates, but data are so far restricted to case reports.7,9,22 It has been suggested that IVIg could lead to faster viral clearance due to pathogen-specific neutralizing antibodies;4 however, the evidence is not yet definitive.23 IVIg samples tested in Japan exhibited significant levels of neutralizing antibodies against HPeV3.23 In laboratory tests, IVIg demonstrated a dose-dependent suppression of HPeV3 replication. Additionally, administering IVIg at an early stage proved to be more effective in reducing HPeV3 RNA levels.24 Other case reports describe improvement of severe
myocarditis and dilated cardiomyopathy secondary to HPeV1 following IVlg treatment, with increased HPeV1 antibody titers being linked to the response observed.8

While the role of corticosteroids in bacterial meningitis is still under investigation, studies from high-income countries suggest that treatment with dexamethasone is associated with lower mortality in adults and fewer neurological and auditory sequelae in children and adults. In contrast, studies conducted in developing countries have yielded ambiguous results.25 While studies from high-income countries suggest benefits in terms of reduced mortality and sequelae, studies in developing countries have not shown consistent results. Further research is needed to understand the factors influencing the effectiveness of corticosteroid treatment and to clarify its potential risks and benefits.25 Our patients were successfully treated with IVlg and corticosteroids with no major neurologic deficits at discharge.

The long-term neurodevelopmental outcomes of HPeV infection have been observed to be heterogeneous, ranging from normative development to varying degrees of cognitive impairment, learning disabilities, behavioral anomalies, severe developmental delays, cerebral palsy, and intractable epilepsy.39 In our report, patient 1 had diffuse hypotonia and moderate developmental delays at seven months old with concerns for seizures for which she is still on Phenobarbital (Table 1). Given the potential risk of neurodevelopmental abnormalities and epileptic seizures, individuals diagnosed with this condition should undergo close follow-ups with pediatric neurologists.

CONCLUSIONS

In this case series, we discuss four cases of severe illness caused by HPeV infection in neonates and young infants during the 2022 nationwide outbreak. Given the lack of antivirals at this time, prompt diagnosis and supportive management are important. In addition to typical supportive measures, IVlg and corticosteroids can be considered as adjunctive therapy in severe HPeV illness, but require more data to support routine use. Seizures can be refractory and may benefit from parental antiepileptic therapies for control. Patients are at risk for long-term neurologic sequelae and need close post-discharge follow-up. Outbreaks should be monitored with active surveillance and research focused on host immunity and anti-viral options are critical to ongoing management of severe HPeV disease, especially in neonates.

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We thank the patients for allowing us to publish this report.

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Case Report

Recurrent Breast Angiosarcoma
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INTRODUCTION

Angiosarcoma of the breast is a rare and typically aggressive malignancy which is responsible for less than 1% of breast malignancies. Primary breast angiosarcoma occurs spontaneously, most often within the third through fifth decade of life, while secondary breast angiosarcoma occurs in women previously treated for breast carcinoma with breast-conserving therapy and radiation or less commonly in the setting of longstanding lymphedema. Primary angiosarcoma of the breast most often presents with a palpable mass which can be rapidly progressive, sometimes with blue or purple skin discoloration, while secondary angiosarcoma typically presents with rash-like skin changes or skin discoloration. The latency period for the development of secondary breast angiosarcoma following radiation treatment is variable with a median of five to six years. Diagnosis is difficult in that mammogram and ultrasound findings for primary breast angiosarcoma are nonspecific, though there is higher sensitivity of detection with ultrasound compared to mammogram. MRI findings can be helpful in the diagnosis of breast angiosarcoma, with typical MRI findings showing high signal intensities on T1 and T2-weighted imaging. Based on the limitations in diagnostic imaging in identifying breast angiosarcoma, a high degree of clinical suspicion is recommended with consideration of biopsy, especially in patients with cutaneous findings that can be missed on imaging.

Given the rarity of breast angiosarcoma, treatment recommendations are predominantly based on expert opinion. The mainstay of treatment has been mastectomy, although there is some evidence suggesting breast conservation surgery results in increased overall survival in primary breast angiosarcoma and non-inferior overall survival in secondary breast angiosarcoma when compared to mastectomy. Radiation therapy has been utilized in treatment of primary and secondary breast angiosarcoma, but evidence for improved survival has not been clearly demonstrated. There is potential benefit for chemotherapy in overall survival for patients with secondary breast angiosarcoma, but this has not been demonstrated in primary breast angiosarcoma.

Prognosis of breast angiosarcoma is poor, with five-year overall survival estimated to be 44.9%. Disease recurrence is common with frequent sites of recurrence being local-regional (32.6%), liver (13.6%), bone (10.5%), and lung (10.5%), with reported disease recurrence occurring at 37 months. In this case report, a patient was found to have recurrent breast angiosarcoma 31 years after treatment for primary breast angiosarcoma.

CASE REPORT

A 78-year-old female with past medical history significant for left primary breast angiosarcoma status post lumpectomy and radiation therapy in 1992 presented to her primary care physician with a two-to-three-week history of skin changes on the left breast. The lesion overall was not bothersome although it occasionally itched and had not displayed significant change since onset. She had no other associated symptoms. Previous mammogram obtained two years prior was stable, with follow-up recommended in one year. Physical exam (Figure 1) of the left breast was notable for approximately 2 cm diameter circular lesion with central eschar at 1 o'clock position from the nipple. No other breast masses or axillary lymphadenopathy were noted. Given her history and presentation she was referred to a breast clinic for biopsy and breast imaging was ordered.

Upon evaluation in the breast clinic, she underwent diagnostic ultrasound and mammogram of the left breast along with a punch biopsy of the lesion. Ultrasound (Figure 2) showed a 2.6 x 0.5 x 3.1 cm subcutaneous mass that was hypoechoic with ill-defined margins and internal vascularity. Pathology was consistent with angiosarcoma. Breast MRI was obtained which showed biopsy proven angiosarcoma with additional suspicious mass and non-mass enhancement in the left breast with concern for metastatic spread of disease given abnormal skin thickening with associated enhancement in the right breast along with irregular enhancing masses within soft tissues of the chest. CT scan of the chest, abdomen, and pelvis (Figure 3) was obtained, which showed widespread metastatic disease throughout the abdomen and pelvis including hepatic, splenic, adrenal, retroperitoneal, osseous, and subcutaneous metastases. She was referred to oncology to discuss treatment options, which unfortunately were palliative in nature given the widespread extent of her disease at presentation. Treatment options presented included conventional chemotherapy with taxane-based agent, tyrosine kinase inhibitor, or immunotherapy with shared decision making to proceed with the tyrosine kinase inhibitor sunitinib.
Figure 2. Ultrasound of left breast showing 2.6 x 0.5 x 3.1 cm subcutaneous mass that was hypoechoic with ill-defined margins and internal vascularity [Figure used with patient's consent].

Figure 3. CT scan with contrast showing hepatic and osseous metastases [Figure used with patient's consent].

Approximately one month into treatment she presented to the University of Kansas Health Center’s emergency department with nausea, vomiting, diarrhea, and progressive weakness with inability to care for herself at home. She underwent evaluation of diarrhea without identification of infectious etiology and GI symptoms were felt to be secondary to chemotherapy side effects and sunitinib was held on admission. Repeat CT scans showed stable to mild progression of disease. During her hospitalization she had acute onset of urinary retention with significant lower extremity weakness and decreased rectal tone. She underwent MRI of her lumbar spine with and without contrast (Figure 4) which revealed enhancing multifocal osseous metastatic disease with extraosseous extension of the tumor at the L2 vertebral body, along with spondylolisthesis and concomitant spondylotic change at L4-L5 with resulting marked trefoil type stenosis [Figure used with patient's consent].

Post-operatively she had improvement in her lower extremity strength. Urinary retention remained an ongoing issue and an indwelling Foley catheter was placed. She developed haimatemesis with acute blood loss requiring transfusion post-operatively. She underwent EGD which showed grade D esophagitis with pathology negative for HSV and CMV. Given the number of medical issues facing the patient, palliative care was consulted, and patient elected for discontinuation of cancer treatment with a goal of improving strength with transition to care focused on maximizing quality of life. She completed a stay at a skilled nursing facility with improvement in her lower extremity strength and resolution of her neurogenic bladder.

DISCUSSION

This case report describes a patient with a history of primary breast angiosarcoma initially treated with lumpectomy and radiation who developed a late recurrence of breast angiosarcoma which was diagnosed at an advanced stage. Patients who have undergone radiation therapy for treatment of breast cancer are at increased risk for the development of secondary breast angiosarcoma. The pathophysiology of radiation-associated breast angiosarcoma is not well understood and it displays a variable latency period ranging from 6 months to 41 years with an average of six years. Risk factors for development of secondary angiosarcoma include increasing age, White race, invasive tumor, lymph node removal, history of lumpectomy, and history of radiation therapy.

Radiation-associated secondary breast angiosarcoma typically presents with cutaneous findings, which can often be missed on surveillance mammography. A retrospective review of patients with radiation-associated breast angiosarcoma showed sensitivity rates of mammography at 43%, ultrasound at 50%, MRI at 92%, and CT scan at 84%. Although this represents a limited data set of patients, it underscores the need for both patients and physicians to have a high degree of suspicion for patients presenting with cutaneous skin changes, especially in patients...
with a history of breast radiation, and proceeding with biopsy when needed, even considering reassuring breast imaging. Treatment recommendations for both primary and secondary breast angiosarcoma are based on case series due to the overall low incidence of the disease. Overall survival rates are better for primary breast angiosarcoma versus secondary, with lack of demonstrated difference in outcomes of treatment with surgery alone versus a combination of surgery and chemotherapy or surgery and radiation therapy. Development of secondary breast angiosarcoma is extremely rare, with estimated cumulative incidence of 1 per 1,000 in patients with breast cancer who underwent radiation therapy. Rates of breast conserving treatment with radiation therapy have been increasing, resulting in an increased population of patients at risk. Given this patient's history, she had potential for recurrence of primary breast angiosarcoma and for development of secondary breast angiosarcoma secondary to treatment, but given the latency period and presentation, it is likely she developed secondary breast angiosarcoma as a sequela of her breast radiation. 

CONCLUSIONS

Breast angiosarcoma is a rare malignancy with challenges in detection and treatment compared to other types of breast cancer. Patients with a history of radiation therapy are at increased risk for development of secondary breast angiosarcoma that can present with isolated cutaneous changes that may not be detected with mammography. Patients and physicians should maintain a high degree of suspicion in the investigation of skin changes which occur in women with a history of radiation therapy. 

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REFERENCES

Case Report

Lipoic Acid as a Trigger for NELL-1 Positive Membranous Nephropathy
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INTRODUCTION

Membranous nephropathy (MN) occurs when antibodies target an antigen in the glomerular basement membrane (GBM). Primary membranous nephropathy (PMN) represents 70% of MN cases1 with M-Type Phospholipase A2 Receptor (PLA2R) being the target antigen in about 70% of cases, Thrombospondin type-1 domain-containing 7A (THSD7A) in about 1-5% of cases, and about 25% of cases having an unknown target antigen.2 Recently, nerve epidermal growth factor-like 1 (NELL-1) antigen-antibody has been identified as a rare cause of PMN in PLA2R-negative cases.2 Lipoic acid, an over-the-counter supplement commonly used to manage neuropathic pain, has been linked to triggering NELL-1-associated MN, resulting in high-grade proteinuria.3 Discontinuation of lipoic acid showed best results in some patients, as they achieved full remission within six months.4

CASE REPORT

A 67-year-old woman with a history of type 2 diabetes mellitus for 16 years, chronic kidney disease, and peripheral neuropathy was referred by her primary care physician due to high-grade proteinuria (4,175 mg/24 hours) and peripheral edema. Her serum creatinine level was 11 mg/dl. The patient had been taking lipoic acid supplements for the past few years to treat her diabetic neuropathy, which provided relief from neuropathy symptoms. Further investigations, including chest x-ray, kidney ultrasound, anti-nuclear antibodies (ANA), serologies for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), anti-PLA2R, and anti-THSD7A antibodies, were inconclusive. A kidney biopsy revealed the characteristic features of NELL-1-associated MN (as shown in Figures 1 and 2). As NELL-1 is associated with malignancy, a thorough screening for cancers yielded negative results.5 Consequently, the lipoic acid supplements were discontinued, and monthly follow-ups with renal function testing were initiated. After discontinuing lipoic acid, urine albumin excretion improved to 675 mg/24 hours after two months and further decreased to 228 mg/24 hours at five months. The patient’s last serum creatinine level was 0.92 mg/dL.

DISCUSSION

NELL-1 antigen presence in membranous nephropathy can indicate the development of secondary membranous nephropathy associated with malignancy or serve as an underlying cause for primary membranous nephropathy, specifically NELL-1-associated MN.6 The latter form is characterized by the presence of autoantibodies targeting the NELL-1 protein within the glomerular basement membrane.7 Recognition of NELL-1-associated MN cases relies on the identification of distinctive histopathologic features. These features include a granular capillary loop pattern observed during Immunoglobulin G (IgG) and IgG1 subclass staining, exhibiting a segmental to incomplete global distribution.7 This case report highlights the significance of recognizing NELL-1-associated MN as a distinct clinical entity, as it can inform treatment decisions and provide insights into prognostic factors. Lipoic acid, a potent antioxidant commonly used in the management of diabetic neuropathy and other medical conditions, has been implicated in the development of NELL-1-associated MN, although the precise mechanisms remain unclear.8 The existing literature is limited, primarily consisting of a few case reports that highlight the association...
between lipoic acid and MN. Approximately one-third of patients with NELL-1-associated MN have a history of malignancy, with detectable levels of serum NELL-1-antibodies. However, further investigations are necessary to determine the potential correlation between antibody levels, the presence of proteinuria, and the underlying malignancy.

CONCLUSIONS

This case report suggests that lipoic acid supplementation may trigger the development of NELL-1-associated MN. Patients taking lipoic acid supplements and presenting with symptoms of kidney disease should be evaluated for this rare condition. Further studies are needed to investigate the potential link between lipoic acid and NELL-1-associated MN.

REFERENCES


Keywords: lipoic acid, primary membranous nephropathy, NELL-1-associated membranous nephropathy, nephrotic syndrome
**INTRODUCTION**

Succinylcholine is one of the most used drugs in anesthesiology and is the only depolarizing neuromuscular blocker in use today. It allows for rapid intubation and is often used in emergency situations where quick airway access is necessary. However, its use can lead to hyperkalemia, a condition characterized by elevated potassium levels in the blood. The potential for hyperkalemia is especially concerning in patients with pre-existing kidney disease, as they may already have elevated potassium levels.

**CASE REPORT**

Our patient was a 42-year-old male who presented as a Level II trauma activation after sustaining a crush injury with a steel beam to the abdomen. Per emergency medical services personnel, the patient was pinned under the 25-foot beam for approximately 10 minutes. He subsequently underwent five additional abdominal operations under general anesthesia for debridement and wound vacuum changes without incident.

On hospital day 30, the patient was brought to the OR once again for final closure of his abdominal wound. He was attached to standard physiologic monitors and pre-oxygenated with 100% FiO2 via bag mask ventilation. Venous access consisted solely of a 24-gauge in the right hand, and the decision was made to proceed with this line through induction and place a larger gauge catheter once the patient was asleep. Anesthesia was induced with 5 mL lidocaine, 100 mcg fentanyl, and titrated doses of propofol to a total of 200 mg. The patient was a difficult bag-mask secondary to facial hair and jaw clenching. A 9 cm oral airway was placed with achievement of satisfactory ventilation, and 100 mg succinylcholine was then administered. An initial attempt at direct laryngoscopy proved difficult and was aborted secondary to desaturation to 63%; he was manually ventilated back to 100% and a second attempt at direct laryngoscopy was successful. Controlled ventilation was initiated, and the tube was taped in place while another anesthesia provider began looking for a second intravenous (IV) site. During this period of time the patient was noted to have peaked T-waves that were not found on pre-operative electrocardiogram (EKG) that quickly progressed to a wide–complex rhythm. Systolic blood pressure was noted to be about 70 mmHg and was unreadable on a recheck. Disorganized electrical activity was then noted on EKG with pulsatile wave form on plethysmography. A pulse check was performed at the carotid artery and no pulse was observable.

At this time chest compressions were initiated, and a code blue was called. Pharmacy was notified for treatment of presumed hyperkalemia. The patient’s 24-gauge peripheral IV was no longer able to flush and was thought to have infiltrated sometime after induction. An IV attempt in the left external jugular vein was unsuccessful. Bilateral groins were prepped by surgery and a left central line was placed, along with a right femoral arterial line for pressure monitoring. One gram calcium gluconate was pushed, followed by 25 g of dextrose with 10 U of insulin, and 360 mcg of albuterol were delivered through the endotracheal tube. Return of spontaneous circulation was noted nine minutes after initiation of chest compressions and the code was called off. Systolic blood pressure following these interventions was 210 mmHg and returned to pre-induction values of about 140 mmHg over a course of a few minutes. EKG displayed normal sinus rhythm. Inhalational anesthetic was discontinued, and the patient was switched to spontaneous respirations on the ventilator. He demonstrated appropriate tidal volumes and respiratory rates and was extubated without incident. He was transported to the ICU and upon arrival the patient was GCS 15 and in no apparent distress. Labs were drawn on arrival to the ICU and showed a potassium of 3.9, compared to a pre-operative value of 4.1. The patient was taken back to the OR the following day for final closure of his abdominal wound. He was discharged to inpatient rehabilitation three days following the events described above.

**DISCUSSION**

The case above highlights the reversibility of hyperkalemia-induced cardiac arrest. Imperative to success in this example was the quick recognition of perioperative problems and multidisciplinary team work to initiate appropriate treatment modalities. As will be discussed below, this case also highlights numerous topics for further research, more
founded guidelines, and potential innovation.

Succinylcholine has been found to raise serum potassium levels by 0.3-1.0 mEq/L when administered in induction doses ranging from 0.5-1.0 mg/kg in patients with normal potassium levels prior to administration.9,16 Hyperkalemia can lead to adverse cardiac effects and manifests as changes on EKG. These changes include peaked T-waves, diminished P-waves, widened QRS, and various arrhythmias including atrioventricular blocks, bradycardia, ventricular tachycardia, and ventricular fibrillation.5-8 Cardiovascular instability usually occurs at potassium levels > 8 mEq/L, though values of more than 11 mEq/L have been recorded without any cardiovascular complications.9,10

Though our patient appeared to show a step-wise progression from peaked T-waves to a wide-complex rhythm and ultimately pulseless electrical activity, EKG changes occur in a variable fashion and some patients with coexisting electrolyte abnormalities/pathologies, such as hypercalcemia, hypernatremia, alkalemia, myocardial ischemia, intraventricular conduction delay, and end-stage renal disease may exhibit no EKG changes secondary to the effect of disease-related fluctuations in calcium levels.11

Early and aggressive correction of potassium levels is an important first step when hyperkalemia-related cardiac arrest is suspected. Literature supports initial treatment with 1-2 g calcium chloride or gluconate to act as a cardiac membrane stabilizer prior to correction whenever EKG findings are first noticed.12 Nebulized or inhaled β2-agonists and 1 ampule of D50 with 10 U of insulin IV promote potassium shift from the extracellular space into the intracellular compartment and represent the mainstay of treatment. The use of sodium bicarbonate to enhance intracellular shift is controversial.12,13 These therapies have a quick onset of action and are temporizing measures that have been shown in studies to significantly lower potassium levels within 30 minutes.12 We did not obtain lab values during the arrest in our case, yet labs drawn 71 minutes after the event revealed a normal potassium level of 3.9 mEq/L, compared to a pre-operative level of 4.1 mEq/L.

Notably, most of the literature discussing succinylcholine use after trauma describes patients with pre-existing elevated potassium levels (e.g., pathology involving an upregulation of post-junctional acetylcholine receptors). These patients are particularly susceptible to succinylcholine-induced hyperkalemia 24-72 hours following traumatic injury.14 Our patient was never found to have an elevated potassium level throughout his entire hospital stay, nor did the day of the cardiac arrest fall within the aforementioned time frame. Also, according to the FDA-approved drug label for succinylcholine, patients in the acute phase of injury show a susceptibility for hyperkalemia, which peaks at 7-10 days after the event.15 This is due to both receptor upregulation and the influence of rhabdomyolysis on intracellular potassium release.16,17 Receptor upregulation is a manifestation of both increased numbers of acetylcholine receptors which spread to the surface membrane outside of the NMJ and a change in receptor subunit type from ε to γ, which represent an immature form through which potassium efflux is magnified.16,17 Rhabdomyolysis is a breakdown in skeletal muscle membrane function leading to loss of cell contents including potassium and creatinine kinase (CK), and has been found in one study to result in a higher chance of unsuccessful resuscitation and thus conveys a greater risk than that related to receptor upregulation.16

Our patient was 30 days post-injury and still showed clinical evidence of hyperkalemia despite normal pre-operative potassium levels. His CK was only mildly elevated, reaching a peak of 1,194 U/L, early in his course and was resolved by the time of our encounter. Although the precise timeframe and duration of the risk period for hyperkalemia are 7-10 days, the upregulation of receptors can persist as long as the underlying condition that produced it continues to exist.9,15 Furthermore, recovery of muscle dysfunction can be delayed as long as one to five years following critical illness requiring an ICU stay.16,17 It is important to note, however, that our patient had received succinylcholine during induction of anesthesia four days prior to our event with no noted complications. In light of this, we felt reasonably confident that the patient had surpassed the window of susceptibility and thus could be administered succinylcholine safely.

Also unique to our case was the very rapid recovery experienced, with just nine minutes of advanced cardiovascular life support (ACLS) performed before return of spontaneous circulation. Succinylcholine-induced hyperkalemia often lasts 10-15 minutes,20,21 however, some have a significantly longer (up to 90 minutes) timeframe before successful recovery.22 The reasons behind the high inter-individual differences in recovery time remain unclear. Basic science studies have postulated this variability to the distribution of acetylcholine receptor and the degree of their mRNA expression,23 with a higher number of receptors distributed throughout more muscle tissue resulting in more long-lasting and profound hyperkalemia. Other theories speculate about differences in AChR isomer activity, specifically the α7AChR, exhibiting a continuous potassium leak leading to the persistence of cell depolarization and a longer timeframe for recovery.24

A search of the National Anesthesia Clinical Outcomes Registry revealed the incidence of cardiac arrest associated with anesthesia to be 5.6 per 10,000 cases.25 The incidence of hyperkalemia in hospitalized patients is estimated between 1 and 10 in 100 admitted patients.26 While hyperkalemia-induced cardiac arrest remains infrequent, cardiac arrest in the perioperative period carries a significantly higher (30.5-80%) survivorship compared to inpatient arrest (10%) in other areas of the hospital.27 This can likely be explained by the unique milieu in which anesthesiologists encounter such circumstances. In contrast to patients on the wards, those in the OR are constantly monitored, with real-time information available regarding changes in EKG rhythm, end-tidal CO₂ respiratory pattern, and circulatory status. All of this allows for near immediate feedback of treatment success or failure and thus significantly higher ACLS survirviorship. Of note, this case highlights the importance of appropriate consideration of vascular access before induction of anesthesia. Our patient had a 24-gauge peripheral IV as his only access upon arrival to the OR. His resuscitation was complicated by the infiltration and loss of this route during ACLS, which could have greatly affected the outcome of our interventions.

In conclusion, EKG changes, in association with a patient at risk
for hyperkalemia, demands immediate recognition by the provider. Anesthesia-centered ACLS and prompt treatment utilizing additional care teams is paramount to successful intra-operative resuscitation. With the recent approval and increasing availability of sugammadex as a reversal agent for rocuronium, the use of succinylcholine is likely to decrease. However, anesthesiologists must remain vigilant in the perioperative period to achieve positive outcomes in even the most critical situations.

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Keywords: hyperkalemia, cardiac arrest, succinylcholine

Presentations: This case report was presented with an abstract at the Midwestern Anesthesia Residents Conference in 2018 in Cincinnati, Ohio.
Tranexamic Acid in Foot and Ankle Surgery: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction. Tranexamic acid (TXA) use has become common in orthopedic surgeries. Despite the growing number of publications related to its use, no recent systematic reviews have been published examining TXA use in foot and ankle surgery. The purpose of this review article is to provide a summary of the current available literature regarding TXA use in foot and ankle surgery and to further the understanding of its safety and efficacy.

Methods. This systematic review utilized PubMed, Ovid, CINAHL, Clinical Key, Medline, and Embase, and the search was conducted through December 22, 2022. Key words used in the search included: “tranexamic acid,” “TXA,” “foot,” “ankle,” “calcaneal,” and “surgery.” The outcomes within the studies analyzed included measures of perioperative blood loss (intra-operative blood loss, 24-hour post-operative blood loss, blood loss from hour 24 to hour 48, post-operative hemoglobin [Hgb], and post-operative hematocrit [Hct]), as well as wound complications and vascular events. Meta-regression was included to assess the impact of age on between-study variation.

Results. Ten studies met preliminary inclusion criteria. Upon further inspection, eight met full inclusion criteria for the meta-analysis. Despite a growing amount of literature on the topic, there is still a paucity of literature published on TXA use in foot and ankle surgery. Current literature suggests that foot and ankle surgery patients treated with TXA may have reduced 24-hour post-operative blood loss (MD=183.41 mL, 95% CI=-247.49 to -119.34 mL, p<0.001), increased post-operative hemoglobin (MD=0.71 g/dL, 95% CI=0.11 to 1.31 g/dL, p=0.020), and hematocrit (MD=2.66%, 95% CI=0.07 to 5.24%, p=0.040) when compared to similar patients not receiving TXA. The use of TXA in foot and ankle surgery did not lead to increased thromboembolic complications. Meta-regression indicated no clinically relevant association of age to between-study variation.

Conclusions. TXA was found to be a safe treatment that did affect wound healing or infection rates while decreasing perioperative blood loss. Further research should be performed to evaluate the long-term effects of TXA administration on patient outcomes after foot and ankle surgery. Kans J Med 2023;16:302-308

INTRODUCTION

Tranexamic acid (TXA) is an anti-fibrinolytic drug that has been utilized in both surgical and non-surgical settings for decades.1 Non-surgically, TXA is used to prevent excessive bleeding during menstruation and epistaxis.2 Originally, TXA was utilized postpartum and in gastrointestinal (GI) surgeries and has since seen expanded indications, becoming a mainstay in many orthopedic procedures around the country, especially in total joint arthroplasty and trauma. The clinical rationale behind TXA use in surgery is the reduction of intra-operative and post-operative bleeding, subsequent reduction in wound complications, and improvement in patient outcomes.1

To our knowledge, two systematic reviews have been conducted on the use of TXA in foot and ankle surgery, with the most recent study’s data collection period ending in January 2022. A main conclusion of both reviews was the need for expanded literature to arrive at a definitive conclusion on the safety and efficacy of TXA use in foot and ankle surgery.3,4 Since the publication of the most recent review article, additional studies have been published, and a larger body of evidence is now available. The aim of this review article is to provide a summary of the current available literature regarding TXA use in foot and ankle surgery and to further the understanding of its safety and efficacy.

METHODS

Search Strategy. A reviewer (N.D.) performed a systematic review according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as outlined on the PRISMA checklist. Databases utilized included PubMed, Ovid, CINAHL, Clinical Key, Medline, and Embase, and the search was conducted through May 21, 2022. Key words used in the search included: “tranexamic acid,” “TXA,” “foot,” “ankle,” “calcaneal,” and “surgery.” The basic search performed on Ovid utilized its related terms function. The search was repeated on December 22, 2022, to gather data that had been published since the original search. A flowchart of the systematic review process is presented in Figure 1.
Inclusion and Exclusion Criteria. The following inclusion criteria were utilized in identifying eligible studies for the systematic review: randomized controlled trials (RCT), cohort studies, case-control studies, and case series examining TXA use in foot and ankle surgery; studies listing the number and type of surgeries performed; studies specifying the dosage and timing of TXA administration; studies published during or after 2000; studies performed on humans; studies published in English; peer-reviewed; and full text available. The only additional inclusion criterion for the meta-analysis was the use of a comparison group within the study. Exclusion criteria for the systematic review included: studies published before 2000; studies not performed on humans; studies not published in English; studies not peer-reviewed; and reviews, individual case studies, technique papers, or opinion pieces. The only additional exclusion criterion for the meta-analysis was a lack of a comparison group as statistical analysis could not be run. Using these criteria, the titles of all papers identified during the literature review were screened by one reviewer (N.D.). Any paper not meeting the inclusion criteria for study design were excluded. The abstracts of the remaining papers were screened and full texts of any works that had not met exclusion criteria were reviewed. Papers included by the first reviewer were screened and confirmed by a second reviewer (J.E.). The outcomes within the studies analyzed included measures of perioperative blood loss (intra-operative blood loss, 24-hour post-operative blood loss, blood loss from hour 24 to hour 48, post-operative hemoglobin [Hgb], and post-operative hematocrit [Hct]), as well as wound complications and vascular events. Wound complications and vascular events were defined as infection, hematoma formation, necrosis, dehiscence, deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), acute coronary syndrome (ACS), cardiovascular event (CVA), limb ischemia (LI), gastrointestinal hemorrhage (GIH), nerve damage, and any other conditions specified as wound complications or vascular events within individual studies.

Data Preparation. Data extraction was performed by two authors (J.E. and N.D.). The Cochrane Collaboration’s Risk of Bias 2 (RoB2) tool was used to assess the risk of bias in the studies included. The RoB2 tool uses five domains to critique how a RCT was conducted and produces an overall rating of either low risk of bias, some concerns of bias, or high risk of bias.3 The quality of the studies included was scored using the Coleman methodology score (CMS).4 The CMS grades studies with a maximum score of 100. Studies receiving a score greater than 85 are excellent, 70–84 are good, 55–69 are fair, and less than 55 are poor.7 Due to the short-term nature of the studies included in this review, the CMS was modified (MCMS) by excluding the second and seventh sections of the CMS. This created a maximum score of 85, so MCMS values were divided by 85 and converted to a score out of 100 so that the qualitative designations of the CMS could be used.

Statistical Analysis. Primary treatment outcomes having data from three or more studies available were summarized in forest plots using RevMan 5.4.1 software (The Cochrane Collaboration, Copenhagen, Denmark). Random-Effects models were used to calculate mean differences with 95% confidence intervals for each outcome measure. Heterogeneity of studies was assessed using Chi-squared ($\chi^2$) and I² statistics. For studies reporting outcomes as median, range, and sample size, means and standard deviations were estimated using methods described by Hozo et al.9 Meta-Regression was conducted in R (R Foundation for Statistical Computing, Vienna, AT) to test for the covariate effect of age between studies and was done using standardized within-study group averages for each outcome analyzed. Statistical significance was set at $\alpha=0.05$ for all comparisons.

RESULTS

Literature Search. The initial literature search produced 1,125 papers, 38 of which were duplicates and removed. The titles of the remaining 1,087 papers were screened and 526 studies were excluded. The abstracts of the remaining 561 studies were screened and 545 excluded. The full texts of the remaining 16 studies were assessed using the inclusion and exclusion criteria established above. Seven studies met preliminary inclusion criteria.9-15 Upon further inspection, five met full inclusion criteria for the meta-analysis, and two articles were excluded from the meta-analysis due to lack of a comparison group.6-1013-17 The second literature search produced an additional three studies that met full inclusion criteria for the meta-analysis, two of which were newly published, and one that had been incorrectly excluded during the initial search.16-18 This process is illustrated in Figure 1.

Study Characteristics. Eight studies with a combined 362 patients treated with TXA and 376 controls met inclusion and exclusion criteria for the meta-analysis.9-1013-18 An additional two studies met inclusion and exclusion criteria for the systematic review and had a combined 266 patients who received TXA.11-12 One study contained two experimental groups receiving different doses of TXA.15 A summary of the studies can be seen in Table 1.

Modified Coleman Methodology Score. The MCMS scores of the included studies are displayed in Table 2. Two studies had excellent scores, two good, one fair, and five poor. The overall grade of the studies included within the meta-analysis was fair, and the overall grade of the studies included within the systematic review was fair.

Risk of Bias 2 Tool. The results of the RoB2 assessment are displayed in Figure 2.
Table 1. Study characteristics.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study (Level of Evidence)</th>
<th>n</th>
<th>Age (mean in years)</th>
<th>Procedure</th>
<th>TXA Route</th>
<th>TXA Dose</th>
<th>Included in Meta-analysis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali et al., 2022</td>
<td>Retro. Cohort (3)</td>
<td>33</td>
<td>67.2?</td>
<td>Total Ankle Arthroplasty IV</td>
<td>1-2g</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>B. H. et al., 2021</td>
<td>RCT (1)</td>
<td>49</td>
<td>51.2</td>
<td>*</td>
<td>IV</td>
<td>10mg/kg body weight</td>
<td>Yes</td>
</tr>
<tr>
<td>Huang et al., 2022</td>
<td>RCT (1)</td>
<td>20</td>
<td>43.9</td>
<td>Calcaneal Fx Fixation Irrigation</td>
<td>100 ml 0.5g/L</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Moore et al., 2022</td>
<td>Retro. Cohort (3)</td>
<td>101</td>
<td>59.4</td>
<td>**</td>
<td>IV</td>
<td>20mg/kg body weight</td>
<td>Yes</td>
</tr>
<tr>
<td>Nodzo et al., 2018</td>
<td>Retro. Cohort (3)</td>
<td>25</td>
<td>65.8</td>
<td>Total Ankle Arthroplasty IV</td>
<td>1g</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Steinmetz et al., 2020</td>
<td>Retro. Cohort (3)</td>
<td>55</td>
<td>62.7</td>
<td>Total Ankle Arthroplasty IV</td>
<td>2g</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Xie et al., 2015</td>
<td>RCT (1)</td>
<td>45</td>
<td>43.4</td>
<td>Calcaneal Fx Fixation IV</td>
<td>15mg/kg body weight</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Zhong et al., 2021</td>
<td>RCT (1)</td>
<td>17</td>
<td>43.1</td>
<td>Calcaneal Fx Fixation IV</td>
<td>200mg</td>
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<td></td>
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<tr>
<td>Zhong et al., 2021</td>
<td>RCT (1)</td>
<td>17</td>
<td>40.4</td>
<td>Calcaneal Fx Fixation IV</td>
<td>400mg</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Johns et al., 2020</td>
<td>Retro. Cohort (3)</td>
<td>241</td>
<td>None</td>
<td>Not specified</td>
<td>*** IV</td>
<td>1g</td>
<td>No</td>
</tr>
<tr>
<td>Sadoun et al., 2021</td>
<td>Retro. Cohort (3)</td>
<td>25</td>
<td>61</td>
<td>Total Ankle Arthroplasty IV</td>
<td>1g</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

* Bunionectomy, Ankle arthrodesis, Sesamoidectomy, Ankle fracture fixation, Tibia/fibula osteotomy, Hallux valgus fixation, Ankle replacement, Mid-foot fusion, Hindfoot osteotomy, Flatfoot reconstruction
** Arthroplasty, Subtalar fusion, Ankle fusion, Double arthrodesis, Tibiotalocalcaneal fusion, Triple arthrodesis, Pantalar fusion
*** Trauma ankle hindfoot and ankle, Trauma midfoot/forefoot, Arthrodesis, Tendon repair/transfer, Elective reconstruction midfoot/hindfoot, Elective reconstruction forefoot, Infection/tumor, Amputation, Arthroscopy, Nerve Surgery, Arthroplasty, Hardware removal

Table 2. Modified Coleman Methodology Scores (MCMS).

<table>
<thead>
<tr>
<th>Study</th>
<th>CMS</th>
<th>MCMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali et al., 2022</td>
<td>44</td>
<td>52</td>
</tr>
<tr>
<td>B. H. et al., 2021</td>
<td>66</td>
<td>78</td>
</tr>
<tr>
<td>Huang et al., 2022</td>
<td>74</td>
<td>87</td>
</tr>
<tr>
<td>Moore et al., 2022</td>
<td>53</td>
<td>48</td>
</tr>
<tr>
<td>Nodzo et al., 2018</td>
<td>48</td>
<td>56</td>
</tr>
<tr>
<td>Steinmetz et al., 2020</td>
<td>40</td>
<td>47</td>
</tr>
<tr>
<td>Xie et al., 2015</td>
<td>75</td>
<td>88</td>
</tr>
<tr>
<td>Zhong et al., 2021</td>
<td>67</td>
<td>79</td>
</tr>
<tr>
<td>Johns et al., 2020</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>Sadoun et al., 2021</td>
<td>40</td>
<td>47</td>
</tr>
<tr>
<td>Average of 10 studies in systematic review</td>
<td>54.3</td>
<td>62.4</td>
</tr>
<tr>
<td>Average of 8 studies in meta-analysis</td>
<td>58.4</td>
<td>66.9</td>
</tr>
</tbody>
</table>
Calcaneal Fracture Fixation. Three RCTs examining TXA use in calcaneal fracture fixation were included in the review. The studies included a total of 183 subjects, 99 of whom were treated with TXA. Huang et al. published a study examining topical application of TXA during calcaneal fracture fixations using the extended lateral approach. Statistically significant findings included a decrease in 24-hour post-operative drain volume in the TXA group (63.3 vs. 181.0 mL, p < 0.001), 48-hour post-operative drain volume in the TXA group (73.8 vs. 210.3 mL, p < 0.001), and hemoglobin reduction (4.6 vs. 12.6 g/L, p < 0.001). Hospital length of stay and hematocrit change were both reduced in the TXA group, though the difference was not statistically significant. No wound complications were reported in either group. The study concluded that topical application of TXA during calcaneal fracture fixation was safe and effective at reducing post-operative blood loss and did not lead to wound complications.

In 2015, Xie et al. published a study of 90 patients that investigated TXA use in calcaneal fracture fixation. Twenty-four-hour post-operative blood loss was found to be significantly decreased in the TXA group (110 vs. 320 mL, p < 0.001). Additionally, post-operative hemoglobin (12.82 vs. 11.57 g/dL, p < 0.001) and post-operative hematocrit (36.1% vs. 33.9%, p = 0.0008) were found to be significantly higher in the TXA group. The study concluded that TXA had significantly fewer wound complications (3 vs. 10, p = 0.036), but similar rates of vascular events (4 vs. 2, p = 0.673) and adverse side effects (3 vs. 1, p = 0.306). Adverse effects reported in the TXA group included one case of deep vein thrombosis, one case of acute coronary syndrome, and two cases of GIH. Adverse effects reported in the non-TXA group included one case of deep vein thrombosis and one case of GIH. The other outcomes measured failed to produce statistically significant results. Xie et al. concluded that a single dose of preoperative TXA could reduce post-operative blood loss and wound complications, without an increase in side effects following calcaneal fracture fixation.

Zhong et al. published a RCT of 53 patients that investigated the use of TXA during surgical fixation of Sanders III-IV calcaneal fractures. All surgeries were open reduction internal fixation (ORIF) via extended lateral approach. The RCT consisted of three groups. Group A consisted of 17 subjects, group B consisted of 17 subjects, and group C consisted of 19 subjects. Group A received 20 mL of 10 mg/mL TXA solution, group B received 20 mL of 20 mg/mL TXA solution, and group C received 20 mL of sterile saline. A statistically significant decrease (p < 0.001) in 24-hour post-operative blood loss was found in both group A (110 mL) and group B (130 mL) compared to group C (360 mL). Post-operative hemoglobin and hematocrit levels were also found to be significantly higher (p < 0.008 and p < 0.001, respectively) in group A (12.3 g/dL, 38.1%) and group B (12.2 g/dL, 37.8%) in comparison to group C (10.8 g/dL, 32.2%). The remaining outcome measures failed to reach statistical significance. Group A and B each had three cases of wound complications, and group C had four. This study concluded that TXA use could effectively reduce post-operative blood loss, but did not significantly reduce wound complications when injected via drain following ORIF of Sanders III-IV calcaneal fractures.

Total Ankle Arthroplasty. Four studies with 263 subjects have been published examining TXA use in total ankle arthroplasty. All four were retrospective reviews. Nodzo et al. published a study of 50 patients that examined TXA use in total ankle arthroplasty. The study was a retrospective review and included 25 subjects who received TXA and 25 who did not receive TXA. Patients who received TXA were given 1 g IV 20 minutes prior to tourniquet deflation. Post-operative blood loss was estimated from total drain output. Calculated blood loss was significantly reduced in the TXA group compared to the non-TXA group (649.9 mL vs. 906.8 mL, p = 0.010). Two wound complications were reported in the TXA group, and five were reported in the non-TXA group, though this difference was not significant. The study concluded that TXA could be used to decrease post-operative hemarthrosis and reduce the risk of post-operative wound complications in total ankle arthroplasty.

Steinmetz et al. published the second study in 2020. The study was a retrospective chart review of 119 patients who underwent total ankle arthroplasty, of which 35 received 1 g TXA IV prior to tourniquet inflation and 1 g TXA IV following tourniquet deflation. No outcome measure reached statistical significance. There were eight intra-operative and nine post-operative complications in the TXA group, and six intra-operative and five post-operative complications in the non-TXA group. Post-operative complications in the TXA group included five early wound complications (prior to three months), two late deep infections (after three months), and two patients with dorsal foot numbness. Post-operative complications in the non-TXA group included one early wound complication (prior to three months), one pulmonary embolism, two patients with dorsal foot numbness, and one patient with component malposition. The study concluded that TXA use may not be effective in reducing intra-operative blood loss, perioperative blood loss, transfusion rate, or wound complications in total ankle arthroplasties.

The third study was a 2021 retrospective review by Sadoun et al. The primary goal of the study was to establish the efficacy of an outpatient total ankle replacement protocol. The chart review included 25 patients who had undergone an outpatient total ankle replacement, all of whom were treated with 1 g TXA IV preoperatively and 1 g TXA IV post-operatively. The primary outcome measures of the study were not pertinent to the scope of this review. However, secondary outcomes of post-operative drain volume and wound complications were measured and reported. An average of 94.6 mL of drainage was measured per patient prior to discharge, and only one wound complication was recorded in the study. No conclusions pertinent to TXA use were made.

Ali et al. published the last study in 2022. The study was a retrospective chart review of 69 patients who underwent total ankle arthroplasty, of which 33 received 1-2 g TXA IV prior to tourniquet inflation. The only outcome that demonstrated significant results was wound complications, of which the TXA group showed a reduction. Four wound complications were reported in the TXA group, whereas eight were reported in the non-TXA group (p < 0.002). The study concluded that TXA use is safe, though a larger sample size is needed to conclude that it reduces wound complications.
Multi-Surgery Studies. Three studies with 553 patients, and a total of 558 surgeries, investigated TXA use in patients who underwent a variety of foot and/or ankle surgeries. B. H. et al. published an RCT of 49 subjects that received TXA and 51 subjects that did not receive TXA during 1 of 10 different surgeries. The TXA group received 10 mg TXA/kg body weight IV prior to surgical incision and the control group received 10 mL saline/kg body weight IV prior to surgical incision. The only outcome found to be statistically significant was a reduction of intra-operative fentanyl consumption in the TXA group (0 vs. 50 mcg, \( p=0.03 \)), although the study questions the clinical significance of this finding. No other reported measure reached statistical significance. The TXA group had a total of eight wound complications and two other adverse effects. The control group had eight wound complications and one case of nausea/vomiting. Neither group reported any vascular events. B. H. et al. concluded that TXA use did not positively influence the measured outcomes, though there were no serious adverse effects.

Johns et al. published a retrospective review of 241 patients who received 1g TXA IV 10 minutes prior to surgical incision of 1 of 12 different types of foot or ankle surgeries. One case of superficial cellulitis, one deep operative site infection, four cases of delayed wound healing, one deep vein thrombosis, and two pulmonary emboli were reported. The study concluded that a preoperative bolus of TXA administered IV in foot and ankle surgeries was associated with a low risk of wound complications, infections, hematomas, thromboembolic events, and overall complication rates with minimal side effects.11

Moore et al. published a retrospective review of 212 subjects who had one of seven different types of foot or ankle surgeries. Five subjects underwent two surgeries each. TXA was administered in 101 of the 217 surgeries within the study. Subjects in the TXA group received 20 mg/kg body weight TXA IV prior to tourniquet deflation. The main outcome examined within this study was wound complications, though Moore et al. performed statistical analysis on individual categories of complications, which was not examined within this review. Within the TXA group, there were less infections requiring antibiotics, cases of delayed wound healing, reoperations, and wound complications in general. The study concluded that TXA has a favorable side effect profile and that its use should be considered in hindfoot/ankle fusion surgeries and total ankle arthroplasties.

Intra-operative Blood Loss. Three included studies examined intra-operative blood loss, though none found statistically significant differences between TXA and non-TXA groups.2,10,16-17 Combined analysis of the three studies (Figure 3) produced no statistically significant difference in intra-operative blood loss between TXA and non-TXA groups (MD = 2.3 mL, 95% CI = -5.89 to 10.50 mL, \( p=0.580 \)). Heterogeneity was high (\( I^2=84\% \), \( \chi^2 =0.002 \)), which suggests a large amount of difference between studies. Meta-Regression indicated age did not have a statistically significant influence on the effect sizes (\( I^2=91.82\% \), \( R^2=0.00\% \), \( p=0.566 \)). The residual heterogeneity is likely attributed to the differing methods of measuring intra-operative blood loss and the inclusion of different surgeries.

**Figure 3.** Pooled analysis for effect of TXA on intra-operative blood loss (mL). Estimated means and standard deviations (SD) for Steinmetz et al. calculated according to Hozo et al. Abbreviations: nTXA - no TXA; CI - confidence interval.

Post-operative Blood Loss. Four included studies with a total of five groups receiving TXA examined 24-hour post-operative blood loss.\(^{10,14,15,18}\) Three included studies with a total of four groups receiving TXA examined blood loss from 24 to 48 hours.\(^{10,14,15}\) All five groups receiving TXA had statistically significantly lower blood loss values at 24 hours. Pooled analysis (Figure 4) produced a statistically significant decrease in 24-hour post-operative blood loss (MD = -183.41 mL, 95% CI = -247.49 to -119.34 mL, \( p<0.001 \)) with low heterogeneity (\( I^2=28\% \), \( \chi^2 =0.240 \)) suggesting agreement between studies. Meta-Regression indicated age did not have a statistically significant influence on the effect sizes (\( I^2=41.53\% \), \( R^2=0.00\% \), \( p=0.568 \)).

**Figure 4.** Pooled analysis for effect of TXA on 24-hour post-operative blood loss (mL). Abbreviations: nTXA, no TXA; SD, standard deviation; CI, confidence interval.

Zhong et al. found a statistically significant increase in blood loss from 24 to 48 hours in their A group (TXA) versus non-TXA. No other groups had statistically significant differences between TXA and non-TXA groups. Combined analysis (Figure 5) produced no statistically significant difference in post-operative blood loss from 24 to 48 hours between TXA and non-TXA groups (MD = 1.42 mL, 95% CI = -5.21 to 8.04 mL, \( p=0.670 \)). Moderate heterogeneity (\( I^2=68\% \), \( \chi^2 =0.020 \)) suggested some differences between studies. Meta-Regression indicated age had a statistically significant influence on the effect sizes (\( I^2=0.00\% \), \( R^2=100.00\% \), \( p=0.002 \)), however, the data indicated high collinearity and clinical relevance of this finding was unclear given the lack of association in intra-operative and 24-hour values. All blood loss values were below a relative low value of 42 mL, which may have contributed to the difference between studies. Blood loss values that may not be clinically significant, even if statistically significant.
Post-operative Hemoglobin. Five included studies with a total of six groups receiving TXA examined post-operative hemoglobin.\(^9\)\(^{13-16}\) Xie et al.\(^{14}\) and both Zhong et al.\(^{15}\) groups demonstrated statistically significant higher values of post-operative hemoglobin in patients who received TXA versus patients who did not receive TXA. Huang et al.\(^9\), Steinmetz et al.\(^{13}\), and Ali et al.\(^{16}\) did not find statistically significant differences in post-operative hemoglobin values. Pooled analysis (Figure 6) produced a statistically significant difference in post-operative hemoglobin in TXA groups versus non-TXA groups (MD=0.71 g/dL, 95% CI=0.11 to 1.31 g/dL, p=0.020). Heterogeneity was high (I\(^2\)=73%, \(\chi^2\) p=0.002), which suggested a moderate amount of difference between studies. Meta-Regression indicated age did not have a statistically significant influence on the effect sizes (I\(^2\)=77.37%, R\(^2\)=0.00%, p=0.994).

**Post-operative Hematocrit.** Four included studies with a total of five groups receiving TXA examined post-operative hematocrit.\(^9\)\(^{13-15}\) Xie et al.\(^{14}\), and both Zhong et al.\(^{15}\) groups demonstrated statistically significant higher values of post-operative hematocrit in TXA groups versus non-TXA groups (MD=2.66%, 95% CI=0.07 to 5.24%, p=0.040). Heterogeneity was high (I\(^2\)=86%, \(\chi^2\) p<0.001), which suggested a large amount of difference between studies. Meta-Regression indicated age did not have a statistically significant influence on the effect sizes (I\(^2\)=46.96%, R\(^2\)=0.00%, p=0.462).

**Wound Complications and Vascular Events.** Eight included studies with a total of nine groups receiving TXA measured wound complications and vascular events.\(^9\)\(^{13-18}\) None found statistically significant differences between TXA and non-TXA groups. Combined analysis of the eight studies (Figure 8) produced no statistically significant difference in wound complications and vascular events (MD=0.71, 95% CI=0.43 to 1.16, p=0.170). Heterogeneity was low (I\(^2\)=37%, \(\chi^2\) p=0.130), which suggested agreement between studies. Meta-Regression indicated age did not have a significant influence on the effect sizes (I\(^2\)=46.96%, R\(^2\)=0.00%, p=0.462).

**DISCUSSION**

Our findings demonstrate that TXA use in foot and ankle surgery does not appear to increase the incidence of wound complications and vascular events when compared to patients not treated with TXA. In addition, patients treated with TXA had lower post-operative 24-hour blood loss, and higher post-operative hemoglobin and hematocrit values when compared to patients not treated with TXA. Age was not found to have a significant impact on effect sizes for between-study heterogeneity, which suggests that treatment factors, such as sample collection methods and surgery type, are more likely associated with variations. An influence of age on 24 to 48-hour blood loss was indicated in our findings; however, this finding is difficult to interpret given the abnormal nature of the blood loss amount reported, as well as the lack of influence of age on blood loss at other time points.
Our findings do not support the postulation that decreased perioperative blood loss reduces the risk of wound complications in foot and ankle surgery. Correlation between perioperative blood loss and infection rate have not been studied in foot and ankle surgery. It is the authors’ suggestion that future research be conducted into the relationship between perioperative blood loss and infection rates in foot and ankle surgery, as the current sample size in the literature is not large enough to determine a difference or to state that no difference occurs.

All trials examining hemoglobin and hematocrit values demonstrated reduced post-operative decrease in hemoglobin and hematocrit.10-13-16 Without the complete data set from each individual study, analysis to determine statistical significance of these variables could not be completed. As such, post-operative hemoglobin and post-operative hematocrit were used as proxy measurements for perioperative blood loss instead.

Current literature suggests that foot and ankle surgery patients treated with TXA may have reduced 24-hour post-operative blood loss, increased post-operative hemoglobin and hematocrit when compared to similar patients not receiving TXA. There is no current data supporting the supposition that TXA use improves wound healing or infection rates, though the use of TXA in foot and ankle surgery did not lead to increased thromboembolic complications. Use of TXA in foot and ankle surgery should be determined on a patient-by-patient basis. Further increased thromboembolic complications. Use of TXA in foot and ankle surgery.

REFERENCES


Keywords: Tranexamic acid, foot injury, ankle injury, surgical blood loss, wound healing

Conflicts of Interest. Dr. Damon Mar has served as a consultant for Agada Medical and Texas Back Institute. Dr. Bryan Vopat has served as a consultant for Artelon and holds a role within the American Orthopaedic Foot and Ankle Society.
