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Prehospital Clinical Decision-Making for Medication Administration for Behavioral Emergencies

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ABSTRACT

Introduction. Prehospital behavioral emergency protocols provide guidance on when a medication may be necessary for prehospital behavioral emergency. However, the final decision of which medication to administer to a patient is made independently by paramedics. The authors evaluated circumstances in a prehospital behavioral emergency when paramedics considered chemical restraints, and factors that go into choosing which medications to administer.

Methods. A qualitative research design was used involving paramedics from a Midwestern County in the United States, between November 18 and 26, 2019. A total of 149 paramedics were asked to complete a survey consisting of two open-ended questions to measure their clinical decision-making process and factors considered when selecting a medication from a behavioral emergencies protocol. An immersion-crystallization approach was used to analyze the content of the interviews.

Results. There was a 53% (n = 79) response rate. Six major themes emerged regarding the paramedics' decisions to use medication for behavioral emergencies: safety of the patients and paramedics, inability to use calming techniques, severity of the behavioral emergency, inability to assess the patient due to presentation, etiology of the behavioral episode, and other factors, such as age, size, and weight of the patient. Six major themes emerged regarding factors considered when choosing medication for behavioral emergency: etiology of the behavioral emergency, patient presentation, the patients' history and age, desired effect and intended outcome of the medication, and other factors.

Conclusions. Emergency medical services (EMS) paramedics relied on several factors, such as safety of all parties involved and etiology of the behavioral emergency in deciding when, and which medication to use in a behavioral emergency. The findings could help EMS administrators to develop protocols, such as how paramedics respond and treat patients with behavioral health emergencies. ***Kans J Med 2023;16:189-193***

INTRODUCTION

Behavioral emergencies are complex situations in which affected individuals, due to an interplay of factors such as intoxication, agitation, pain, psychosis, and/or other mental illness, may be at risk of harm to themselves and those around them.[1-3] From June 2017 through May 2018, approximately 6% of emergency medical services (EMS) cases in the United States were behavioral emergencies.[4] In some of the cases, a combination of physical and chemical restraints (e.g., haloperidol, lorazepam, ketamine, midazolam) were used. The use of physical restraints, however, in the prehospital setting has potential adverse outcomes, such as sudden death, severe acidosis, going into a state of excited delirium, or a combination of these factors.[5-7]

Deciding how to manage a behavioral emergency requires cautious and thorough consideration.[1,3] EMS personnel have a responsibility to balance the safety of the patient and themselves, relying on context clues of their surroundings in the pre-hospital setting.[8,9] Paramedics who arrive on the scene of a patient experiencing behavioral episodes often have limited information and must act quickly for well-being of the patient, making it difficult to determine what factors are playing into the behavioral emergencies.[4] In such situations, quick decisions must be made by paramedics to determine treatment modality, which, unfortunately, can contribute to negative patient outcomes, such as misdiagnosis of the patient, miscalculation in dosages, and subsequent deaths.[2,10] Therefore, the clinical decision-making protocol for using chemical restraints must be more standardized. Chemical restraints are medications often used for behavioral emergencies to "subdue, sedate, or restrain" patients.[11,12]

States and counties have their own protocols for how to assess and manage behavioral emergencies of adult and pediatric populations, although most operate on a continuum of increasing intervention.[4] When managing behavioral emergencies, initial safety measures may include verbal communication and require that a law enforcement officer is present. More dangerous situations may require the use of physical restraints before resorting to chemical restraints.[3,4,13] However, no gold standard protocol has been developed for paramedics to decide when to use chemical restraints and which type of medications to use during a behavioral emergency. In addition, there have been no known studies on the factors that influence paramedics' clinical decision-making regarding the use and choice of chemical restraint. Therefore, this study sought to describe the circumstances in a behavioral emergency when paramedics consider chemical restraints, and factors that play into choosing which medications to administer.

METHODS

Participants. The study involved a convenience sample of 149 EMS paramedics from a large Midwestern county in the United States. Participation from all paramedics in the county were solicited by email from November 18 through 26, 2019. No paramedics were excluded. The participants did not receive an incentive for completing the survey.

Instrument. No demographic information was collected to protect anonymity and to improve the likelihood that paramedics would complete the survey. The novel survey included two open-ended questions. First, respondents were prompted to report what impacts their decision to use or not to use medication when caring for a patient experiencing a behavioral emergency. Second, respondents were asked to report what factors they consider when choosing the type of medication to give during behavioral emergencies.

Procedures. This study was approved by the University of Kansas

Medical Center's Institutional Review Board. A literature search yielded no similar instruments that met the needs of the study. A survey consisting of two open-ended questions was developed to measure the paramedics' clinical decision-making process and factors that they considered when selecting a medication from the behavioral emergencies protocol. A multi-stage process was utilized to confirm the validity of the questions. First, questions were created based on the goal of the study and were reviewed by an emergency medicine physician to ensure that they accurately assessed the proposed constructs. Next, expert reviews in the form of vetting the questions were conducted by an emergency medicine resident physician, a clinical practice manager from the county's medical director's office, and a paramedic to ensure the questions met the goal of the study. To ensure that the questions were worded correctly and that they could solicit the needed information, the authors also conducted a cognitive interview with two paramedics.[14] Unlike regular interviews where respondents are asked to recall an event or information, cognitive interviews are an evidence-based, qualitative method used to evaluate whether survey questions solicit the needed information. Those paramedics who helped corroborate the questions did not participate in the study.

SurveyMonkey®, an online survey platform, was used to create the survey and generate an electronic survey link that was distributed to the paramedics' professional e-mail addresses. The survey was sent by a faculty member from the University of Kansas School of Medicine-Wichita and prompted participants to complete the two-item questions. To enhance the number of respondents, two e-mail reminders were sent one week apart to all potential participants, unless they opted out of the survey.

Statistical Analysis. The authors analyzed the data using an immersion-crystallization qualitative approach to analyze the content of the open-ended responses individually and as a group.[12-14] The immersion-crystallization approach offers researchers the opportunity to examine collected data in detail and periodically suspend the immersion process to reflect on emerging findings until consistent themes are identified.[15-17]

RESULTS

The response rate was 53% (n = 79). Six major themes emerged regarding the paramedics' decisions to use medication for cases involving patients with behavioral emergencies: safety of patients and paramedics, inability to use calming techniques, severity of the behavioral emergency, inability to assess the patient due to presentation, etiology of the behavioral episode, and other factors, including the age, size, and weight of the patient (Table 1). Regarding safety, paramedics considered the threat that the patients may pose to themselves and/or to the paramedics and crew. The inability to assess the patient because of any erratic or hostile behavior included a subtheme of the patient's escalation of those behaviors.

Six major themes emerged regarding the factors paramedics consider when choosing which medication to use in a behavioral emergency. These themes included: etiology of the behavioral emergency, patient presentation, patient's history and age, desired effect and intended outcome of the medication, and other factors. The patient's history included subthemes regarding their medical, behavioral, and illicit or prescribed medications. Other factors included subthemes regarding the vitals and weight of the patient, ease of administration, potential adverse effects or allergies to the medication, comfort level with the medication, distance to the hospital, and balancing the risk and benefits of the medication (Table 2).

DISCUSSION

To our knowledge, this is the first published study of its kind specifically assessing factors that influence paramedics' clinical decision-making regarding the use and choice of chemical restraint. The findings of the study showed that EMS paramedics relied on several factors, such as safety of patients and paramedics, inability to use calming techniques, severity of the behavioral emergency, inability to assess the patient due to presentation, and etiology of the behavioral episode, when deciding whether to use medications in a behavioral emergency. These findings may offer insights into developing protocols regarding how paramedics respond and treat patients with behavioral emergencies. The finding regarding safety of the patients and paramedics as the most common theme that drives paramedics' decision to use medication for a patient experiencing a behavioral emergency was consistent with results of previous research that suggested that medications are administered based on behaviors that may predispose paramedics or the EMS service to danger, such as agitation or aggression.[3,13]

The EMS personnel in this study emphasized that their decision to use a chemical restraint depended on etiology and severity of the behavioral episode. Given that every situation is different in terms of etiology and severity, prior preparation for potential dangers and organizing a care plan with the entire team, including law enforcement, can protect all those involved.[18,19] Using a risk assessment tool, such as the Richmond Agitation Sedation Score or Altered Mental Status Score, could assist with assessing such situations and choosing the optimal approach to safely subdue agitated patients or those with an altered mental status.[20] Creation of a crisis intervention team where paramedics coordinate with mental health clinicians and trained local police departments, may target repeat behavioral emergency dispatches with appropriate behavioral health care as a preventive measure to future interactions may be beneficial.[21,22]

Findings about the use of calming techniques prior to using medications to sedate patients in our study were in line with results from prior studies that suggested verbal de-escalation techniques can reduce the risk of progression of agitation into violence and such approaches need to be considered prior to chemical and physical restraints.[1,23,24] Although the paramedics in the current study did not specify the type of calming techniques they often use, prior research suggested that clinical shared-decision making with firm boundaries between the clinician and the patient was the most effective way to avoid mistrust and escalation of erratic or hostile behaviors, which may allow for paramedics to assess and evaluate the patients better.[17,23,24] Our findings also found that patient demographics, such as age, were considered prior to medication administration. This information was consistent with the suggestion that patients older than 65 years need to be evaluated for signs of acute confusion or delirium.[20]

Table 1. Paramedics' open-ended comments on decision to use medication for behavioral emergency.

Themes	Subthemes	Quotations from Participants
Safety	Safety of paramedics	"First, I consider the safety of myself and my crew. If the patient appears to be extremely agitated and potentially violent, I will err on the side of medication every time."
		"If I am in fear for my safety or the safety of my partner then I will use medication"
	Safety of the patient	"...if the patient cannot be safely reasoned with, is hurting themself, or my team then medication is the safest route for everybody."
		"Primarily the decision is based on the threat the patient poses to herself or responders."
Unsuccessful use of calming techniques		"I move to medications only when I am unable to use calming techniques."
		"When patient is capable of calming with reassurance and calming techniques resulting in normalizing of vital signs and ceasing any behaviors likely to cause harm to self or others, no medication is used."
Severity of the emergency		"When de-escalation fails then safety must take priority and the patient is then restrained and/or sedated."
		"The patient's presentation and the likelihood of the patient's status changing during transport."
		"Pts whose anxiety, agitation or psychosis is negatively [affecting] their vital signs and coaching/calming techniques have been ineffective."
		"...severity of behavioral emergency and respiratory status."
Inability to evaluate the patient because of erratic or hostile behavior		"If the assessment that we need to do is hindered by the patient's behavior."
		"If the patient is unable to be consoled or able to follow even basic commands to ensure safety then that will also weigh into my decision to administer a medication."
		[Patients] "whose anxiety, agitation or psychosis prevents continuing care including treatment and transportation."

Table 2. Open-ended comments on factors participants consider when choosing medication for behavioral emergencies.

Themes	Subthemes	Quotations from Participants
Etiology of behavioral emergency		"I would consider the etiology of the event."
		"I consider the root cause of their behavior, if it is primarily a psychotic episode..."
		"I consider whether or not this is truly a behavioral emergency or whether or not other substances are involved."
Patient presentation		"...patient presentation and cause of the current behavioral emergency will depend on what is given."
		"Patient presentation and history"
		"I chose medication based on intoxicating substance, patient history, and presentation."
Patient's history	Medical	"Patient's medical history."
		"Past history and medications also are helpful."
	Behavioral	"I ask family, friends or bystanders about patients mental health history as well as current medications."
		"I consider whether they have a psychiatric history."
		"If it is a combative patient due to mainly behavioral problems."
	Illicit or prescribed medication	"What their medical history is, if they are currently on any type of drugs or alcohol, how severe of a physical threat they are."
		"...what medications the patient currently takes and/or is allergic to"
Patient's age		"The [patient's] age will help direct my decision."
		"I consider age..."
Desired effect of medication		"...the desired effect we are looking for."
Intended outcome		"Desired effects of the medication."
		"My intended outcome" [of the medication]
		"..., the treatment goal."

Table 2. Open-ended comments on factors participants consider when choosing medication for behavioral emergencies. *continued.*

Themes	Subthemes	Quotations from Participants
Other factors	Patient's vitals	"There are several factors that I consider when choosing which medication to give. Patient age, medical history, current medications, psychiatric history, ...vital signs."
	Weight of the patient	"I consider age, weight and if any other substance[s] are already on board."
	Ease of administration	"Ease of administration" [of the medication]
	Potential adverse effects and/or patient's allergies to the medication	"Indications/contraindications of the medications [and] potential for adverse effects."
		"Least amount of side effects and usually the quickest acting with route being administered."
	Comfort level	"My comfort level with the medication."
	Distance to hospital	"First, the distance/time from the hospital."
	Risk/benefit of meds	"Which medication will benefit the patient the most with the fewest risks or adverse side effects."

Our study found that the participating paramedics consider six factors, such as safety of patients and paramedics, etiology of the behavioral emergency, patient presentation, patient's history and age, and desired effect and intended outcome of the medication, when deciding which medication to use in a behavioral emergency. The findings regarding physical safety of patients and paramedics were consistent with prior research that documented the physical safety of everyone present during the encounter, including the EMS personnel and patient, should be the predominant factor to consider when managing behavioral emergencies.[13,25] The decision to use, and the type of, medication should depend on factors like etiology of the behavioral emergency, as well as how the patient presents at the time of the emergency.[13] Assessment for intoxication or abnormal changes in behavior, as well as a quick evaluation of the patient's airway, breathing, and circulatory status need to be considered prior to medication administration.[20]

In our study, desired effects and intended outcomes of the medications, as well as the patient's history were reported as factors paramedics consider in deciding which medication to use in behavioral emergencies. These findings were consistent with results of previous studies that indicated medication administration must address the patients' underlying etiology for the behavioral episode quickly and safely by relaxing the patients without making them unconscious.[23,26] In addition, studies suggested that factors related to the medication, such as the side effects and benefits, route and ease of administration, and availability of the medication must be considered.[23,24] These factors also were reported in our study. Calming such patients allows for EMS personnel and other clinicians to obtain vital history and treat any psychiatric-related behaviors. The findings of this study have shown that EMS personnel consider several factors, often unique to each situation or call, when they respond to calls involving behavioral emergencies.

Although the identified factors in this study were consistent with findings from previous studies,[1,3,13,23,24] our study was unique for two reasons. First, it assessed the circumstances in a behavioral emergency when paramedics consider chemical restraints. Second, it examined the factors paramedics considered when choosing the type of medications to administer to such patients suffering from behavioral episodes. To our knowledge, the clinical decision-making process regarding these two circumstances have not been identified and integrated prior to this study, which provided insight into paramedic decision-making.

EMS personnel and organizations would benefit from additional research across the United States to confirm these initial findings and identify other considerations when intervening in a behavioral health emergency. The identification of these factors could allow for consensus-building among paramedics, regionally and nationally, to develop protocols that offer better, more uniform support to patients experiencing suspected behavioral emergencies.

Limitations. This study has several limitations. One major limitation was the absence of demographic information from the participating paramedics. Having this information could help to determine if the sample's demographic information was representative of the population and offer insight into the differences in paramedics' experiences. A new paramedic may work from what they have learned throughout school and from their mentor, whereas a paramedic with years of experience may have responded differently based on their experiences in the field. Also, 70 of the paramedics in the county did not participate in the survey, which creates a potential bias between responders and nonresponders. Inclusion of responses from these additional participants could have provided a more detailed, clearer picture of the use of chemical restraints in this county. There are possible changes to the findings since the data used in the study were collected in 2019, albeit important results. Finally, our findings represented information from paramedics of one county in Kansas and may be applicable to other counties or states with comparable communities and population characteristics.

Future studies could include paramedics across larger areas or multiple regions to confirm our findings and identify other potential decision points and factors involved when intervening in a behavioral health emergency.

CONCLUSIONS

This study sought to characterize paramedics' perspectives about how they decide when to administer medication in behavioral emergencies and the factors considered in choosing the type of medication to treat such emergencies. The findings suggested that several factors, such as safety of the patients and paramedics, etiology of the behavioral emergency, contributed to paramedics' clinical decision process. Determining reasons why paramedics make these decisions, or factors that influence their decision-making process could help administrators to develop protocols that address a variety of behavioral health emergencies.

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Keywords: paramedics, prehospital emergency care, clinical decision making, qualitative research

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Parental Vaccine Hesitancy in a COVID-19 World: A Qualitative Study of Midwestern Parents' Decisions Regarding COVID-19 Vaccination for Their Children

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ABSTRACT

Introduction. With the launch of the SARS-CoV-2 (COVID-19) vaccines, a new cohort of people exists who do not consider themselves to be completely vaccine-hesitant, but are specifically COVID-19 vaccine hesitant (CVH). There is a need to learn from CVH parents, to ensure their concerns are addressed, and allow them to comfortably vaccinate their children against the COVID-19 virus.

Methods. Surveys were used to identify CVH parents. Using semi-structured interviews, we assessed the attitudes of CVH parents toward COVID-19 vaccination in children. An inductive coding method was used to analyze transcripts and develop themes.

Results. Fourteen parents were interviewed. Seven (50%) had received the COVID-19 vaccine even though they had doubts. Six reported that education about mRNA vaccine production was helpful in deciding to get vaccinated. Parents were reluctant regarding pediatric vaccination due to lack of long-term studies and concerns about adverse impact on childhood development. Personal physicians were the most trusted source of information and direct conversations with them were the most influential, as opposed to public health leaders like the U.S. Centers for Disease Control and Prevention and the National Institutes of Health.

Conclusions. Our findings suggested that physicians are among the most trusted sources of information regarding the COVID-19 vaccine for CVH parents. Rather than use broad public health messaging and advertising to increase rates of vaccination, further investigation into training health professionals on how to counsel CVH patients effectively may be a higher impact area of opportunity to improve vaccine response rates. ***Kans J Med 2023;16:194-199***

INTRODUCTION

Vaccine hesitancy has been a topic of discussion between physicians and the public since the creation of the smallpox vaccine by Edward Jenner.[1] Over the years, there have been many different reasons for parental hesitation regarding vaccination including doubts surrounding the necessity, efficacy, and potential adverse effects of them.[1,2] With the onset of the SARS-CoV-2 (COVID-19) pandemic and the expeditious roll-out of vaccines, a new cohort has emerged. These individuals do not consider themselves to be vaccine-hesitant in general, but are COVID-19 vaccine hesitant (CVH). This cohort is crucial to learn from amidst current underwhelming vaccination rates among approved pediatric populations.[3]

Prior parental attitudes toward other vaccines are not predictive of parental acceptance or hesitance toward the COVID-19 vaccine.[4] Many CVH parents have been compliant with other vaccines in the past. For example, only 66% of parents who had their children vaccinated with the influenza vaccine for the last two years self-reported themselves as "very likely" to vaccinate their children against COVID-19.[5] This may be because the COVID-19 vaccines have brought many aspects of vaccination development, testing, deployment, and novel technologies into the spotlight. Highly technical and nuanced subjects like the merits of mRNA versus adenovirus vectors are common household discussions, and, more than ever before, parents must take more into consideration when making vaccine-related decisions for their children.

Three survey-based studies identifying root causes for COVID-19 vaccine hesitancy in the United States have been conducted.[5-7] One reported that less than 50% of 1,745 parents would vaccinate their child against COVID-19.[5] To the best of our knowledge, there have been no published qualitative studies that specifically focus on Midwestern parents' COVID-19 vaccine hesitancy. This study will be the first to look at perceptions and hesitancies surrounding COVID-19 vaccinations among a Midwestern parent population, using qualitative methods. The primary objective aimed to identifying educational strategies and interventions that will facilitate adherence to COVID-19 vaccination recommendations and improve vaccine response rates, while allaying specific parental fears and concerns.

METHODS

This study was reviewed by the University of Kansas Medical Center Institutional Review Board prior to commencement of all study activities.

Recruitment of Subjects. Inclusion criteria included adult subjects who were parents of children <18 years of age. Participants were recruited via invitations through social media posts from the accounts of the Department of Otolaryngology and the research team. Subjects also were able to refer others for participation. Within these invitations was a link to an eligibility survey which decided if the participant met inclusion criteria. The survey was used to decide if the parent was considered a CVH parent. There were no financial incentives given to participants. If parents met inclusion criteria and were deemed CVH parents after taking the eligibility survey, they were contacted to set up an interview either in-person or over Zoom®. Participants signed digital copies of consent forms prior to proceeding with the interview. Following consent, each participant completed a demographic survey. A four-month window was allotted for data collection during the summer and fall of 2021. All moderators for the interviews (S.B., J.M., K.G.) had medical and clinical research experience.

Eligibility Survey. There were two components of the eligibility survey. One component was made of four items created by the research team to determine if a respondent was CVH. Within these four items, a parent was deemed CVH if any of their responses showed a degree of hesitancy. This component corresponds with items 3-6 on the

eligibility survey (Appendix; available only online at journals.ku.edu/kjm).

The second component of the eligibility survey was the 15-item, previously validated, Parent Attitudes about Childhood Vaccines (PACV) tool.[8] This component was utilized to demonstrate a parent's degree of hesitancy toward vaccines in general. If a parent scored a ≥ 50/100 on the PACV, they were considered hesitant toward vaccines in general. A 50/100 was chosen as the cutoff because the original author of the PACV determined that the most predictive score that a parents' child would be under-immunized was ≥ 50/100.[9]

Our goal was to identify a population that was hesitant toward the COVID-19 vaccine while not being hesitant toward vaccines in general. So, if a parent scored ≥ 50/100 on the PACV, they were ineligible for the interview. Parental COVID-19 vaccine status was not a component of inclusion criteria because key insights could come from those who received the vaccine amidst doubt.

Semi-Structured Interview. A semi-structured 15-question interview was conducted for each of the participants (Table 1). The questions were designed to explore the behavior, knowledge, and overall attitudes of CVH parents regarding the COVID-19 vaccine.[10] Interviews lasted between 20-30 minutes.

Study survey and demographic data were collected and managed using REDCap® (Research Electronic Data Capture). REDCap® is a secure, web-based software platform designed to support data capture for research studies, providing an interface for validated data capture.[11,12]

Data Analysis. Each interview recording was de-identified and transcribed word-for word using Trint (London, UK) software and verified for accuracy by at least two of the team members. An inductive coding method was used to derive themes from the data. Members from the team individually coded each transcript to determine themes and sub-themes in each of the interviews. A preliminary codebook was developed and revised in iterative rounds until consensus was reached among all team members regarding salient themes and subthemes. Content saturation occurred when no new information or perspectives were mentioned after 14 interviews. After review of theses transcripts, no new themes were detected, and thematic saturation was determined to have occurred as well. The decision was made to stop data collection, as it was determined that the content validity requirements had been met.[13]

Table 1. Semi-structured interview questions.

1. In regards to your family's healthcare and health guidelines, who are people or groups that you trust the most? Why?
   Probes: Your family doctor, CDC, President of the United States, Dr. Fauci
2. If you were to research information on any general vaccine, where are places you would look?
   2b. Follow up: How do you decide information is reliable about vaccines and health information?
3. What has influenced your opinions on vaccines in general up to this point?
   Probes: Personal experience, news and media, medical professionals, family friends, talk a little bit about why you're against the addition
4. What information is needed for you to feel a vaccine is safe?
   4b. Follow up: Do you feel you have different standards for the COVID vaccines?
   Probe: Health leaders saying so? Friends' children get it? Time on the market?
5. Do you think for some people vaccination is necessary, while for others it's not? Why or why not?
6. What information is needed for you to feel a vaccine is necessary?
   Probe: Does it need to be a super deadly disease? Super infectious?
7. Have you ever actively sought getting a vaccine yourself or have you always waited for your doctor to suggest one?
8. How has the coronavirus pandemic itself, impacted your view of vaccines in general, if at all?
   Probes: more positive/negative view of them since the onset of the pandemic, plans for getting the vaccine for children
   8b. Follow up: Has anyone near you gotten the coronavirus? If so, has this affected your views towards the vaccines or the urgency for it?
9. How do you feel information about public health, like vaccines, should be communicated?
   Probes: different social media, news, billboards, more frequent communication, more clear communication, using multiple different outlets of media for communication
   9b. Follow up: What types of media or ways of communication by health professionals, do you feel would help parents feel more confident in the message they are being sent?
10. What are reasons in the past why you allowed your child to get vaccinated?
11. Do you know anyone who has gotten a serious side effect from a vaccine?
    11b. Follow up: If yes, what was the side effect, was it from a COVID vaccine or a different one?
12. Do you have any specific concerns regarding the COVID vaccine?
    Probes: side effects (short or long term), effectiveness, personal belief, cost, research to quick, side effects, efficacy
    12b. Follow up: If they say side effects - what side effects in particular?
13. If participant signals hesitancy towards a specific COVID-19 vaccine, ask this question regarding the vaccine they indicated.
    Question:
    You noted that you were only hesitant toward the [Specific vaccine brand name] vaccine on the survey, what lead to that hesitancy?"
    13b. Follow up: Where did you hear that information?
    13c. Follow up: What would it take to overcome that concern and receive that particular vaccine, if anything?
    13d. Follow up: If the CDC said it was safe and effective for your child's age group?
14. If participant signals hesitancy towards the COVID-19 vaccines for children under 12 years old, ask this question.
    "On the survey, you noted to be hesitant towards the COVID vaccine for under 12 years old, even if the CDC said it was safe and effective. How does age of the child factor into your decision for getting a COVID vaccine or not?"
15. Do you know their school's policy for this upcoming year regarding COVID vaccines? If so, are you satisfied with it?
    Probes: masks, vaccines, negative test required, no sick symptoms

RESULTS

Half of participants overcame hesitations and received the COVID-19 vaccine. These parents are considered COVID Vaccine Hesitant-Received Vaccine (CVH-RV) parents. Those who did not receive the vaccine by the interview date are considered COVID Vaccine Hesitant-No Vaccine (CVH-NV) parents (Table 2).

Table 2. Participant characteristics.

	n = 14	n (%)
Gender		
Female	10	71.4
Male	4	28.6
Race/ethnicity		
White	12	85.7
Annual household income range		
$100,000 or greater	10	71.4
Living demographics		
Suburban	11	78.6
Other	3	21.4
COVID-19 vaccine status		
Received the vaccine (CVH-RV*)	7	50
Did not receive the vaccine (CVH-NV*)	7	50

*COVID Vaccine Hesitant-Received Vaccine; COVID Vaccine Hesitant-No Vaccine

Four main themes emerged from the interviews: (1) Learning Enhances Trust; (2) Need for Long-Term Studies and Effects on Children; (3) Lack of Perceived Need Among CVH-NV Parents; (4) Personal Health Professionals are the Most Trusted. Specific subthemes were identified among CVH-RV and CVH-NV parents as well.

Theme 1 - Learning Enhances Trust. Six of seven CVH-RV parents reported gaining trust in the COVID-19 vaccine after learning about the process of production mRNA technology for COVID-19 vaccines. For example, community events where local scientists explained the safety of mRNA vaccines were impactful. Participant 1 reflected, "I think just being made aware of [mRNA technology] and aware of those things are helpful".

After learning about the mRNA production process, some parents reported increased confidence in vaccinations for children, with the specific age of children no longer playing a large factor. For example, Participant 2 responded, "I don't think [age matters], because only the smallest amount of that [mRNA] fragment goes into your body".

Theme 2 - Need for Long-Term Studies and Effects on Children. When considering the relative newness of the vaccine and giving it to a child, many parents voiced strong hesitancies. Both CVH-NV and CVH-RV parents cited the timeframe from vaccine trials to vaccine approval as a barrier for receiving the vaccine. "It's just the fact that it's so new and we don't know if there could be some long-term, weird side effects that could affect kids growing up" (Participant 3) was a common sentiment heard from multiple parents. Parents often desired a longer follow-up period to assess for adverse outcomes in adults: "It has to be given to adults now and then wait between 5 and 10 years before they give it to children" (Participant 4).

Parents (36%) noted hesitancy after hearing of myocarditis occurring in children post-vaccination or potential fertility issues in females. Other parents simply were not sure how a COVID-19 vaccine would affect children in terms of their development.

Theme 3 - Lack of Perceived Need Among CVH-NV Parents. Through conversations with CVH-NV parents, it was evident there was a lack of perceived need in receiving the vaccine. Some cited it was not a necessity for their family with "how healthy" (Participant 4) they are. Others stated they did not have a strong perceived need because they had "already had the virus" (Participant 7). Due to already contracting the virus, 42.8% of CVH-NV parents felt the vaccine was not going to benefit them.

Even though CVH-NV parents know people who have died of COVID-19 infections, they did not report this increasing their urgency to receive the COVID-19 vaccine.

> *"The way that I try to look at it is that life and death are going to happen anyways, you know, it's just like if you like, some people die from the flu. Some people die from falling down the stairs. You know, some people die falling asleep... so it really hasn't changed my viewpoint of how life is happening." (Participant 3)*

> *"When you look at the list of side effects of [vaccines], 99.9% of them are worse than the things that you're taking to treat. So, if it's not 100%, then I don't want to take it." (Participant 4)*

Theme 4 - Personal Health Professionals are the Most Trusted. Every participant noted their personal physician, pediatrician, or family friend who is a doctor to be the most trusted individual regarding vaccines and healthcare guidance for their family.

4.1 Vaccine-Hesitancies are Mitigated Through Conversations with Health Professionals. Of note, 85% of CVH-RV parents cited at least one conversation with someone in the healthcare field, whether that be a doctor, nurse, or scientist as a key role in easing hesitancies they had toward the COVID-19 vaccine. CVH-NV parents, although still citing their local physicians as their most trusted source for vaccine information, did not report having conversations specifically about the COVID-19 vaccines with healthcare providers when forming their opinion toward the vaccines.

Even though search engines and news stations were trusted by very few as a reliable source of vaccine information, they were reported as one of the first places parents would research information. Participant 4 noted that by searching Google, they can see what the pro-vaccine opinion and the "extremely opposite" opinion are saying about vaccines. By doing this, they were able to make a more "educated decision" that falls between "both ends of the spectrum". This same participant later reported that their personal doctor was still more trusted than search engines.

> *"When I say doctors, I do mean doctors in general -even people that don't treat me and my family. But I mostly trust my own personal doctor. Because of the way that she treats and deals with us, she actually takes the time to listen and talk things through instead of just saying here, you have to do it." (Participant 4)*

Regardless of current vaccine status, parents trusted their family doctor above all things, including the CDC, WHO, and Dr. Fauci. The only specific argument given by government organizations was in explaining the process of mRNA vaccine technology. Simple reassurance from a trusted source, like a local physician, was a large driving factor in improving trust. When comparing government organizations and local physicians, due to the personal connection between the doctor and patient, recommendations from local physicians carried more weight. For example, Participant 8 said, "I think that at the end of the day, people make decisions based on the people they trust, or they know personally".

4.2 Mass advertising and Large Health Organizations Have Less Influence. Parents were unsure of the effectiveness of mass advertising, such as posters, billboards, and radio/television broadcasts, for promoting COVID-19 vaccine uptake. Participant 8 questioned the effectiveness of mass media advertising saying it "lacks a personal touch" and that "it doesn't give a chance for people to ask any questions". Formal recommendations made by government organizations were met with more skepticism.

> *"I think at the beginning of the pandemic, I listened to everything the CDC [and Dr. Fauci] said until there were contradictory things that they were doing. So, then I had to do my research elsewhere." (Participant 4)*

DISCUSSION

As the age-range of eligible recipients of the COVID-19 vaccine expands, it is critical to understand parental attitudes toward the COVID-19 vaccine. Through semi-structured interviews with COVID-19 Vaccine-Hesitant (CVH) parents, four main themes emerged. Of particular relevance during the pandemic, these results emphasized the need to leverage physicians and other providers as trusted front-line sources of information. For example, 85% of CVH-RV parents overcame their hesitations and ultimately became vaccinated due to conversations with their physician. Therefore, physicians and healthcare professionals must be equipped to use evidence-based counseling for vaccine-hesitant parents.[14]

CVH parents, regardless of vaccine status, unanimously cited their local primary care provider as their most trusted source for vaccine information. This is in line with previous literature among parents hesitant to other vaccines.[15-17] Of note, our findings showed that 85% of CVH-RV parents reported a conversation with a healthcare provider regarding mRNA vaccine technology as key in gaining trust in the vaccine. On the other hand, some of these parents considered the CDC, WHO, and Dr. Fauci less trustworthy due to their perception that these organizations might not follow their own recommendations or share contradictory guidelines. Even though perception and approval of governmental organizations varied widely among the population, local physicians were the most trusted among CVH parents.

Surprisingly, mass advertising campaigns and large health organizations were cited by parents as having low efficacy in overcoming vaccine hesitancy. This was in contrast to prior literature which has shown that use of mass media to influence populations to receive even "controversial" vaccines, such as influenza and HPV, is able to produce noteworthy changes in behavior.[18,19] Therefore, this phenomenon may reflect the relationship between organizational presence on social media and public doubts regarding vaccine safety, which may be influenced by foreign disinformation campaigns that contribute to declining vaccination coverage.[20] This "foreign disinformation" hypothesis is further bolstered by a recent study suggesting a negative association between trust in social media and vaccine acceptance among white respondents.[21]

Interestingly, physicians have expressed frustration, vis-à-vis lack of preparedness in engaging conversations surrounding vaccine-hesitancy, often citing a lack of formal training.[22,23] The effectiveness of different counseling strategies for vaccine-hesitant parents have been analyzed in the past.[14,22] As progress continues to be made in finding the best evidence-based strategy for counseling, our findings showed that physicians already have the potential to be effective in conversation with their patients regardless of which method they choose. Thus, rather than investing in mass advertisements to promote vaccine uptake, health systems should consider investing time and resources in formal training. If physicians are given the formal training to feel confident in these difficult conversations with CVH parents, this will allow them to utilize one of their most effective tools: their already-established trust. Further, having formal training will provide tactful approaches of engaging conversation and mitigate erosion of patient confidence. Efforts through organizations such as Project Extension for Community Healthcare Outcomes (Project ECHO) have also shown promise as a potential avenue in acquiring this training.[24] Project ECHO is a collaborative model of medical education and care management that allows primary care physicians to manage complex patients vis-à-vis subspecialty teams that are reachable through telehealth programs.[25] This system allows experts within the fields of immunology or virology to educate clinicians and patients alike, aiming to improve vaccination rates and increase access to immunization services.

Another area of hesitation was a concern for long term side-effects in children and a desire for more long-term research. This was a similar hesitancy noted by parents when the HPV vaccine was released.[26] Fortunately, the CDC continues to report increases in HPV vaccine uptake as it becomes more established.[27] Therefore, although pediatric COVID-19 vaccine uptake was more nuanced, it was reassuring to know hesitancy can be overcome as more data were compiled. CVH parents additionally cited safety concerns for children because they were still in their developmental stages of life. For example, one participant was concerned because her non-communicative infant would not be able to let her know if a complication arose. These concerns reiterated similar findings from quantitative studies assessing reasons for COVID-19 vaccine-hesitancy.[6,7,28,29] These findings showed that physicians and scientists must continue to be persistent in gathering research to dispel parental doubts regarding vaccines bearing effect on the development of children. Parental confidence was built on data, and reassuring data will drive uptake.

To our knowledge, this is the first qualitative study assessing

COVID-19 vaccine hesitancies among Midwestern parents. Data collection took place prior to any government mandates that required the general population to receive the vaccine. It was possible new hesitations formed among CVH parents due to vaccine mandates.

This study was limited by a small sample size composed primarily of white-identifying individuals. Therefore, generalizability to wider, more diverse populations is an important concern. However, our data exhibited significance in light of 2020 U.S. Census data.[30] The census found that many Midwestern states, such as Kansas and Iowa, consisted of primarily white-identifying populations, accounting for 75.6% and 85.9% of the total state populations, respectively. Moreover, published data suggested that in selected samples of white and black populations, each of whom had experienced a similar level of vaccine hesitancy at baseline, black populations may develop intention to receive vaccinations more readily than their white counterparts.[31] There may be a specific cultural component that may be targeted for improved vaccine uptake among populations. Moving forward, the authors acknowledged the significance in acting to dismantle healthcare disparities across diverse populations. Further studies aimed at investigating multifaceted root causes of vaccine hesitancy should be conducted to develop inclusive and comprehensive strategies that can be generalized more widely to diverse populations beyond the Midwestern United States.

Selection bias was a possibility with utilization of a survey-based eligibility method; however, with the use of a prior validated survey for the process, our team was confident that the sample accurately represented our target population. Another limitation was the U.S. Food and Drug Administration fully approving the Pfizer® vaccine after the interviews were conducted. Perhaps some would have had different opinions after the full approval, and it is worth exploring.

CONCLUSIONS

This study highlighted further understanding into the decision-making process of a new cohort of parents with the onset of the COVID-19 pandemic and rollout of vaccines. With new variants of COVID-19 surfacing and hospital admissions increasing among younger populations,[32,33] there was an urgency for parents' concerns to be addressed. Even though it is a novel vaccine, parents shared many hesitancies they have shown in the past with prior vaccines. This cohort was in a unique position because these parents generally have not been contrary to medical recommendations in the past. Our findings showed that parents could overcome COVID-19 vaccine hesitancies through learning about the vaccine from trustworthy sources, such as local physicians. Therefore, more investigation needs to be completed across more diverse populations to explore whether healthcare professionals would benefit from additional training in effectively engaging in conversations with CVH parents over COVID-19 vaccine hesitancies. This training could emphasize tactful and empathetic communication to avoid erosion of parental confidence, which must be an important consideration since frustration among CVH parents was prevalent. Conducting future studies that focus on this group of parents, especially among more heterogeneous populations, is crucial as vaccine policies and guidelines continue to evolve.

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Outpatient Oncology Fall Risk: A Quality Improvement Project

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ABSTRACT

Introduction. Patients receiving cancer treatment are at high risk for falls. No current guidelines or standards of care exist for assessment and prevention of outpatient oncology falls. This quality improvement project's purpose was to 1) describe and evaluate outpatient oncology falls data to determine root cause(s), and develop, implement, and evaluate intervention strategies for future policy refinement, and 2) compare fall rates pre/post implementation of a system-wide Ambulatory Fall Risk Bundle.

Methods. Retrospective data were used to describe and categorize fall incidence for the University of Kansas Cancer Center over 12 months. Further analyses were conducted to describe fall rates per 10,000 kept appointments pre/post implementation of an Ambulatory Fall Risk Bundle protocol. Semi-structured interviews were conducted with medical assistants and nurse managers to evaluate the initiative's impact, staff satisfaction, and recommendations for refinement.

Results. The initial 12-month assessment yielded 58 patient falls retained for further analyses. Most patients were receiving chemotherapy (46, 79%). Common contributing symptoms included dizziness/faintness and weakness (25, 43%). Tripping/falling over a hazard (12, 24%) and falls during transfer (10, 5.8%) also were cited. Subsequent analyses of fall rates indicated no change. Recommendations resulting from the qualitative interviews included: orthostatic vital sign protocol implementation, redesign of the electronic medical record fall risk alert, stakeholder involvement in protocol development, staff training, and related patient education strategies, and the procurement of additional assistive devices/equipment.

Conclusions. System-related policy and culture change, investment in physical and human resource enhancements, and evidence-based protocols are needed to improve outpatient oncology fall rates.

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INTRODUCTION

Patient safety is paramount for providing high-quality healthcare in both the inpatient and outpatient settings, and fall rates are an important quality indicator for nurse-sensitive outcomes.[1-3] However, the primary focus for fall tracking and prevention occurs in the inpatient setting. Very little literature is available concerning risk factors and the prevention of falls in the outpatient setting. On a more specific level, evidence indicates that individuals diagnosed with, and receiving treatment for cancer may be at higher risk for falls than the non-cancer population, particularly those aged 60 and above.[4-7] Potential risk factors include neurotoxic chemotherapy and orthostatic hypotension.[6-8] To date no guidelines to prevent or reduce falls in the outpatient oncology setting have been published, nor is there a standardized assessment tool to assess fall risk in this population. Oncology nurse educators at the University of Kansas National Cancer Institute-designated Comprehensive Cancer Center (KUCC) recognized outpatient oncology falls as a safety concern and partnered with nurse scientists within the School of Nursing to investigate the problem and propose policy change to the cancer center leadership.

An Oncology Nursing Falls Project Team (Project Team) was formed to develop and conduct a quality improvement project. In addition to the oncology nurse educators and nurse scientists, Project Team representation also included the KUCC Quality & Performance Improvement Manager and nursing faculty with qualitative interviewing and analyses expertise. The initial purpose of this quality improvement project was to describe and evaluate KUCC outpatient falls data to determine root cause(s) and to develop, implement, and evaluate intervention strategies for future policy refinement. However, prior to the completion of the planned data collection and analyses, the parent institution (University of Kansas Health System-UKHS) formed an Ambulatory Practice Council. The purpose of this Council was to develop and implement a system-wide Ambulatory Fall Risk Prevention Bundle (Fall Risk Bundle) to "go live" as of September 2020. As a result, the Project Team adapted the purpose of the quality improvement project to also compare KUCC fall rates pre/post Fall Risk Bundle implementation and to assess staff integration of, and satisfaction with, the new policies to further inform recommendations for system change.

METHODS

Setting and Existing Falls Assessment Procedure. University of Kansas Medical Center (KUMC) Human Subjects Committee quality improvement determination was confirmed prior to data collection. The quality improvement project was conducted at the KUCC, which encompasses eight community oncology outpatient clinics throughout the greater Kansas City metropolitan and surrounding areas.

Prior to initiation of the quality improvement project, UKHS institutional policy for outpatient clinics included a Fall Risk Assessment for patients over age 65 or for those with obvious balance/steadiness issues or use of assistive devices at the time of admission. This assessment involved asking patients three screening questions: 1) Have you fallen within the past six months? 2) Do you use an assistive device? and 3) Do you have any limitations in mobility? A "yes" answer to any of the three questions indicated the patient was "high risk" for falls. The high-risk determination triggered a Fall Risk banner in the electronic medical record (EMR) and outpatient clinic staff were instructed to place a yellow fall risk band on the patient's wrist.

Intervention. The UKHS Ambulatory Practice Council Fall Risk Bundle elements and processes are listed in Table 1. The new workflow included identifying all high fall risk patients during pre-visit planning or chart preparation. The chart was to be reviewed by the outpatient clinic registered nurse (RN) for any patients over the age of 65 with a history of falls within the last six months, as well as the potential for impaired balance or mobility. These patient charts would be flagged as a fall risk by ensuring the Fall Risk banner was displayed in the EMR and the Fall Risk Bundle would be implemented when the patient arrived at clinic. An additional element of the new workflow included a process within the EMR to enable Patient Service Representatives (PSR) working at the registration desk to be able to see a report of the fall risk patients. This Department Appointment Report (DAR) displays all patients and their appointment times for the day. A column was added to the DAR to indicate the patient's fall risk status. If the Fall Risk banner was activated in the patient's chart, then the patient would be flagged on the PSR DAR as high fall risk. This workflow was designed so that the PSR would place a yellow high fall risk wrist band on the patient simultaneously with the patient identification band at check in.

Table 1. Fall risk bundle processes.

Process	Role
Identify and Notify	
Patient identified as a high fall risk during pre-visit planning or chart preparation if possible.	RN
Review chart for all patients over age 65, history of fall within the last six months, potential for impaired balance or mobility, use of assistive device, fall history.	RN
Ensure patient is flagged as high fall risk in EMR.	RN
Notify licensed provider at time of patient check-in.	PSR
Ensure Bundle elements are ready when patient arrives in clinic.	PSR
Apply high fall risk yellow wrist band at time of check in.	PSR
Screen	
Screening completed during rooming process.	MA
Assess for additional interventions.	RN
Assess for potential environmental or ambulation concerns.	RN
Assess high fall risk per clinical judgement.	RN
Bundle Physical Elements	
Yellow high fall risk wrist band	PSR
High fall risk flagged in EMR	RN
Yellow triangular high fall risk door flag for room	MA
Keep patient in lowest & safest position	MA/RN
Yellow high fall risk table tent flag	MA
Provide patient education about preventing falls	RN
Consider additional interventions (e.g., arm's reach while ambulating, use of assistive device such as wheelchair or walker)	MA/RN

Note: MA; medical assistant, PSR; patient services representative, RN, registered nurse

Once the patient was roomed, the fall risk screening questions would be completed by the medical assistant (MA) or person rooming the patient. Fall Risk Bundle elements, in addition to the yellow wrist band, included placing a yellow triangular door flag outside the room and a table tent inside the room stating to "leave the patient in the lowest seated position." The RN would then further assess the patient to identify the need for additional interventions related to environmental or ambulation concerns. Clinical judgement can always trump the fall risk assessment if patient does not meet the criteria, but should be considered a high fall risk based on clinical presentation or underlying disease characteristics.

Prior to Fall Risk Bundle implementation, cancer center staff received education about the new protocol by the Oncology Nurse Educators. MAs and RNs also were required to complete a supplemental assignment in the UKHS-hosted online learning and procedural database detailing the new protocol and to score 80% or higher on the associated quiz.

Measures. UKHS policy requires employees to complete a report within the patient safety event reporting system documenting the occurrence of all falls (patient, visitor, employee) and detailing the event and any assessments and/or interventions that were employed.

Data Collection for Falls Incidence and Description Pre-Fall Risk Bundle. The Project Team utilized the UKHS's patient safety event reporting system to determine the number of falls that occurred in the eight KUCC outpatient clinics and related departments (such as lab, radiology, etc.) between November 2018 and November 2019. These data were extracted in May of 2020. Information stored within the UKHS patient safety reporting system was used to develop the data entry form for a semi-structured dataset of outpatient oncology falls variables.

The variables included in structured fields are outlined in Table 2. Unstructured data fields included free text areas to document diagnosis and other contributing factors not listed in the structured fields. Narrative descriptions of the events associated with the fall incidents included in the free text fields were categorized and tabulated. Questions arising during data entry were discussed by the entire team.

Data Collection to Compare Pre/Post Fall Risk Bundle Implementation Falls Rate. To identify the impact of the Bundle, the fall rate was tracked over time and entered into a process behavior chart (Figure 1). The patient safety event reporting system is used to report events that caused, or have the potential to cause, patient harm. Events are ranked on a harm score of increasing severity from 1 through 9, with scores 1-2 being unsafe conditions or near misses (i.e., not reaching the patient), scores 3-5 indicating an event that reached the patient but did not cause physical harm, and scores 6 and above resulting in physical harm to the patient. Our fall rate included any falls with a harm score ≥3 that occurred in an outpatient cancer center-associated department; falls that occurred in shared spaces (such as lobbies and parking areas) were excluded, as those areas could have been frequented by patients seeking non-oncological medical care from practices outside the KUCC, but which share the same facilities (e.g., primary care, urgent care, radiology). Our denominator included any kept appointment in a cancer center department, meaning any physical (or face-to-face) appointment; cancelations and no-show appointments were excluded,

as were any telehealth appointments (since those patients would not be physically present at the practice location). Our monthly rate of falls per 10,000 kept appointments was then plotted on an XmR process behavior chart (aka Shewhart's Control Chart).

Table 2. Data entry form structured field variables.

Fall details	Event date
	Outpatient oncology clinic location
	Fall harm score
	Factors involved in the fall
	Whether fall was witnessed and by whom
	Whether fall was assisted
Person demographics	Category of person who fell (e.g., patient, family, staff)
	Age
	Gender
	Current treatment (e.g., chemotherapy, radiation therapy, targeted therapy, immunotherapy)
Assessments at time of fall	Physiologic measures (e.g., vital signs, blood glucose)
Pre-fall assessments	Pre-fall visit risk assessment date and risk score
Post-fall assessments	Post-fall visit risk assessment date and risk score

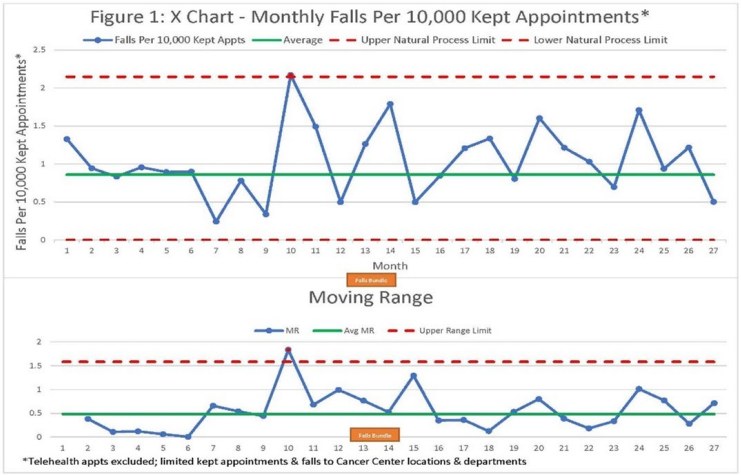

Figure 1. Depicts one X chart and one Moving Range (MR) chart. The upper X chart displays individual measurements of the monthly fall rates over time (per 10,000 kept appointments). The lower MR chart displays the month-to-month variability between corresponding measurements.

Data Collection to Assess Staff Satisfaction with the Fall Risk Bundle Initiative Impact, Related Training, and Recommendations for Refinement. All MAs and nurse managers working in the eight outpatient KUCC clinics were invited by email to participate in this quality improvement project. Participation served as consent, as projects with Human Subjects Committee determination as quality improvement do not require written signature. The sampling goal was to interview all nurse managers and two MAs from each outpatient clinic location, or until data saturation was achieved. Participation for MAs involved virtual attendance at group sessions to provide feedback on the Fall Risk Bundle implementation; nurse managers were interviewed individually. MAs and nurse managers were interviewed separately to facilitate open communication and feedback. Two semi-structured interview guides were developed by the Project Team members with qualitative research expertise (MP). Further revision and approval by the full team was completed prior to use. Parallel questions in the interview guides for MAs and nurse managers were organized around eight categories of interest identified by the Project Team: 1) pre-Fall Risk Bundle falls assessment, 2) Fall Risk Bundle training content, 3) usefulness of Fall Risk Bundle training, 4) suggestions for changes to Fall Risk Bundle training, 5) differences post-Fall Risk Bundle implementation, 6) usefulness of Fall Risk Bundle components, 7) suggestions for changes to the Fall Risk Bundle, and 8) ideas for fall prevention. Interviews ranged from 30-60 minutes and were conducted on a secure Zoom platform after the introduction of the Fall Risk Bundle during the Fall of 2020. The interviews were conducted by one Project Team member (MP) between March and May of 2021. These interviews were recorded, transcribed verbatim (DE) and stored on the institutional password-protected secure computer drive. Member checking was not possible due to pandemic-related staff attrition.

Quantitative Data Analyses. Descriptive statistics (frequencies and percentages) were calculated to describe the falls incidence and associated assessments prior to Fall Risk Bundle implementation (November 2018-2019). Monthly fall rates per 10,000 kept appointments were calculated for the 13 months preceding and following Fall Risk Bundle implementation.

Qualitative Data Analyses. Two Project Team members independently analyzed the written transcripts from the semi-structured interviews (MP, DE). A qualitative thematic analysis with an inductive approach was used to analyze the data. The goal was to evaluate the Fall Risk Bundle initiative impact, staff satisfaction, and recommendations for refinement from the perspectives of the MAs and their nurse managers. The inductive approach was selected so emerging themes were closely linked to the data and not made to fit an existing coding schema.[9] Data analyses were conducted by two Project Team members (MP, DE) who followed the steps outlined by Braun & Clarke.[9] Specifically, data were coded systematically, examined for potential themes and confirmation of how the data reflected those initial themes, followed by the refinement of final themes for reporting.

RESULTS

One systems issue identified by the Project Team during data collection prior to the implementation of the Fall Risk Bundle protocol was the transient nature of the EMR Fall Risk banner. This banner disappeared from the EMR any time a subsequent fall risk assessment did not indicate the patient to be high risk (e.g., the patient did not answer yes to any of the fall risk questions, regardless of whether the patient had a previous fall at the cancer center). Anecdotally, patients were known to refuse the yellow wrist band so as not to be "labeled" as high risk for falls. Additionally, prior to the Fall Risk Bundle implementation, no specific clinic staff role was designated as the one responsible to apply the yellow fall risk wrist band.

Pre-Fall Risk Bundle Description of Falls. The total number of falls were collected for the KUCC eight locations between November 2018 and November 2019. Seventy falls were recorded. After subtracting incidents for staff, visitors, and non-oncology patients, a total of 58 fall incidents were retained for further analysis. Of these 58, 44 patients were determined to have been checked in for their appointment at the time of the fall, 13 had not yet checked in, and the status for 1 was unable to be determined. For the 44 patients who had checked in prior to the fall occurrence, a fall risk assessment was documented for 23 (52.3%), and of these, 7 were found to be low risk and 16 were rated as high risk (Table 3).

Table 3. Fall risk assessment documentation.

	Visit where fall occurred*	Visit preceding fall**	Visit following fall**
Fall risk assessment documented	23 (52.3%)	25 (43%)	32 (72.7%)
Low fall risk rating	7	19	15
High fall risk rating	16	6	17

*Denominator only included the 44 patients who had checked in for their clinic visit prior to the fall.
**Denominator includes the total 58 patients with documented fall incidents.

Data were collected to describe the fall risk assessment results for the outpatient oncology clinic visits preceding and following the fall incidents. Fall risk assessments were documented for clinic visits preceding the fall incident for 25 (43%) patients. Of these 25, 19 were assessed at low risk and 6 rated at high risk. During the clinic visit following the fall incident, fall risk assessments were conducted for 32 (72.7%) patients. At this subsequent visit 17 were rated at high risk and 15 were designated as low risk.

Ages ranged from 39 to 94 (mean age was 65). Most patients were receiving chemotherapy (46, 79%). Alkylating agents were noted to be the most common classification of drugs (16, 34.7%) followed by taxanes (8, 17.4%) and antimetabolites (8, 17.4%). Data were not available on the incidence/presence of neuropathy. Vital signs (including blood pressure and heart rate) post-fall were documented for 10 (17.2%) of the cases. Blood glucose level was documented for one case. The most frequently cited contributing factors to the fall incidents (Table 4) were symptoms described as dizziness, faintness, weakness, and "legs giving out" (25, 43%). Tripping/falling over a hazard was cited for 12 (24%) cases. Falls occurring during transfer (to chair, from exam table, or from car) were cited for 10 (5.8%) cases .

Table 4. Fall incident description.

Fall incident	Frequency
Trip over hazard (or fall over hazard)	12
Trip, no hazard	7
Symptoms (dizzy, faint, weakness, legs giving out)	25*
Transfer (trying to sit, trying to get out of car, trying to get off exam table)	10*
Slip on surface	1
Other	3
Not documented	1

*One case documented dizziness while trying to transfer off exam table.

Comparison of Pre/Post Fall Risk Bundle Implementation Falls Rate. Displayed on the upper X chart of Figure 1 are the individual measurements of the monthly fall rates over time, while the lower moving range (MR) chart displays the month-to-month variability between corresponding measurements. Signals are identified as individual measurements either above or below the upper natural process limit or lower natural process limit, respectively, on the X chart (red, dashed lines), or above the upper range limit on the MR chart (also represented by the red, dashed line). Such a signal (in both the X and MR charts) was identified in month 10, with an increase in the fall rate likely attributable to the clinic expansion that occurred that month in the cancer center, following the COVID-19 lockdown in early 2020. Evidence of a sustained change that occurred to the underlying process would be a signal of exceptional variation[9] and would be represented by eight or more successive measurements on either side of the average fall rate, or the green line on the X Chart. However, as demonstrated by Figure 1, no evidence of a sustained change in the fall rate was noted either before or after the implementation of the Fall Risk Bundle (identified on the chart in month 14). Rather, outside of the clinic expansion signal after the COVID lockdown, the fall rate remained constant around the monthly average of 0.85 falls per 10,000 kept appointments.

Result for the Semi-Structured Interviews. Semi-structured interviews were conducted with 10 of 12 nurse managers (83%) and 21 MAs (minimum target sample of 16). Two or more MA interviews were conducted at all but one site (one interview conducted) and data saturation were achieved. Data analysis revealed concordance between the MAs' perceptions of and experiences with the Fall Risk Bundle and with those of the nurse managers. Goals for the semi-structured interviews were reflected in three main themes that emerged from the data and are outlined below.

Theme 1: Fall Risk Bundle Training - Standard Fare, Although a Good Refresher. In general, MAs and nurse managers remembered few specifics about the Bundle training, although both groups reported the training was a "good refresher."

One MA stated, "I don't think I remember doing it." Another MA said that "if we were assigned [the training] via email, we did it." MAs stated they received many training modules, and a few did remember taking it but not the specifics of the training. Regarding training content, an MA said: "It didn't really add a lot of new stuff from what we previously had. It did help us recall stuff we already knew." Responses to the training were mixed. Some MAs felt they knew the material already and it was repetitive, and others felt it was a good refresher. Some felt the training

was not clinic specific. Satisfaction with the training ranged from neutral to satisfied; one MA said: "I felt it was informative, but it wasn't something that you could put in your memory bank. I just don't think it was powerful enough to stick with you." Other MAs felt it was too long and lacked a "wow factor." Others were more satisfied with the training: "I'm sure I got good information."

Nurse managers found it "hard to gauge [MAs'] engagement, comprehension, retention" of the training information. Nurse managers either did not view the training or did not remember doing so. Some nurse managers believed that the training was a good refresher and useful for new people. Both groups had suggestions for improving the training. MAs stated they wanted in-person, hands-on practice, not a video only; they mentioned the usefulness of a live demo with a mock patient, a group effort, and having someone come in and do the teaching, which would help participants take the content more seriously. One MA said: "In person training is the best so we can see what they want from us. It's more powerful than a test. You can see it and do it." Several nurse managers stated they felt staff learned best from hands-on training while acknowledging that virtual modules that can be completed asynchronously makes training more accessible. Suggestions for improvement included teaching MAs how to address patient education regarding falls prevention, particularly when using the bathroom. Another suggestion was to include a method to measure engagement, comprehension, and retention of material.

Theme 2: Fall Risk Bundle Receives Mixed Reviews. Several MAs felt there was no difference between the new Fall Risk Bundle and the previous procedure, stating "no difference, no change, nothing different." Conflicting opinions were voiced regarding the helpfulness (or not) of the yellow triangles to be placed on the doors of the rooms for patients designated as high fall risk. One MA felt that "hanging something on door is difficult to remember to do in hectic day" while another MA reported a clinic-specific nuance in which all doors already were equipped with metal door flags (red, green, and yellow) so the use of additional yellow door flags was redundant. Additionally, some MAs reported the yellow table tents were a helpful visual reminder of fall risk while others reported these "were too small and got lost".

Nurse managers agreed that there was no real change between the previous procedure and the new Fall Risk Bundle overall, except in signage. One nurse manager said: "The message is just a bit different, and it seems to be louder. Our staff is more alert and aware about it." On the other hand, another nurse manager felt that: "Helping staff understand the why behind the what sometimes can be challenging especially when what's being implemented doesn't make a lot of sense" based on clinic-specific environments. Contrasting opinions about any differences with the Fall Risk Bundle ranged from believing that MAs were more alert and aware about falls, to MAs seeing no value in the Fall Risk Bundle. One manager noted that table tents got in the way of patient care.

Both groups agreed that components of the Fall Risk Bundle were inconsistently implemented across the various outpatient oncology clinics. For example, MAs and nurse managers reported consistent use of the yellow wrist bands as compared to very little uptake for the table tents.

As noted for the Fall Risk Bundle training, both groups shared several pertinent revision suggestions. Broad categories for reduction in fall risk spanned three areas: 1) physical resources, 2) human resources, and 3) process/cultural changes. Physical resource suggestions included: redesign of the EMR fall risk banner to remain in place for six months post-fall regardless of participants' answers to the three fall risk assessment questions, and redesign of the EMR fall risk banner placement in the chart so it is immediately apparent without staff needing to scroll through the chart. Nurse managers also suggested exam tables could be lowered, placement of gait belts in every room, and redesigned bathrooms to provide room for assistive devices and staff while providing privacy. Suggested human resources included implementing a greeter near elevators, escorts to walk patients out of clinic, and developing a process for safely getting patients in and out of the front door. Patient education and culture change around keeping patients safe was noted as necessary to helping patients understand why safety measures were in place – designed for their safety and not meant to diminish their autonomy. Further specifics for suggested revisions are outlined in Table 5.

Theme 3: Fall Risk-Contributing Factors. The most cited location and reason for falls reported by both groups was the bathroom– both as patients traveled to the bathroom and while using it. The underlying issue was noted to be patients' request for privacy in the bathroom and refusal of assistance. Footwear was the second-most cited reason for falls, particularly flip flops. Other places and reasons for falls from the MAs' perspective included patients' disease stage, standing for weight measurement, and lack of education on fall risks. Nurse managers noted sedation medication and refusal to use assistive devices as probable causes. Both MAs and nurse managers agreed that certain physiological factors were likely at play, such as patients being hypotensive, light-headed, or dizzy. Other physical factors identified by both groups included patients tripping over their own feet, tangling with IV poles, and stumbling over poorly placed or designed clinic furniture. Chairs in the clinic rooms were noted to have legs that curved outward, creating a tripping hazard.

DISCUSSION

Evidence-based standards to assess fall risk and prevent falls in outpatient oncology clinics are needed to enhance patient safety. The fall risk screening questions utilized in both the UKHS inpatient and outpatient settings are consistent with falls screening questions recommended by the American and British Geriatrics Societies Clinical Practice Guidelines for Prevention of Falls in Older Persons.[11] However, a recent systematic review of the literature indicates that no standard assessment tool has yet been developed for the outpatient oncology setting.[12] Results from this review demonstrate that a history of falls is the most commonly identified risk factor for older adults with cancer in both inpatient and outpatient settings. Asking about the occurrence of any recent falls is recommended at every clinic visit for this population.

Table 5. Medical assistant and nurse manager recommendations for Fall Risk Bundle revision.

	Medical assistants	Nurse managers
Physical resources	Sturdier/larger fall risk door flags.	Only place fall risk signs/symbols exterior to the room and omit use of table tents.
	Availability/knowledge of location of gait belts.	Supply gait belts in every room.
	Additional (and newer) wheelchairs.	Standardize signs/symbols so that all stakeholders know the meaning. Bathroom redesign to provide room for assistive devices and staff while providing patient privacy.
Human resources	Designated staff (such as transport persons) to assist patients to and from their rooms, and escort them to their vehicle.	Implementation of a greeter near elevators, escorts to walk patients out of clinic, and developing a process for safely getting patients in and out of the front door.
	Conduct daily staff huddles on scheduled patients to identify those known to be high fall risk.	Consistent application of the fall risk wristbands by the registration desk staff prior to patient rooming.
Process/culture change	Availability of additional/enduring training videos.	Development of a falls check list in clinic rooms detailing the steps to prevent falls (such as application of the yellow falls risk wrist band and ensuring patients are placed at the lowest seat/table height).
	Development of a falls check list in clinic rooms detailing the steps to prevent falls (such as application of the yellow falls risk wrist band and ensuring patients are placed at the lowest seat/table height).	Solicitation of stakeholder input from clinic staff, patients, and families prior to further Falls Risk Bundle implementation.
	Implementation of a patient resource guide with focused education about home hazards, footwear, use of handrails in the clinic.	Ensure the Falls Risk Bundle is specific to the cancer patient population and not a "general Ambulatory Fall Risk Bundle".
		Redesign of the fall risk banner within the medical record to remain in place for six-months post-fall; redesign of fall risk banner placement to be immediately apparent without the need for scrolling.
		Patient education and culture change around keeping patients safe (e.g., helping patients understand rationale for existing safety measures).

Since the inception of this quality improvement project, the results of one study have been published describing implementation and study of a color-coded flag system in an outpatient oncology infusion center to reduce fall rates.[13] Shah reports use of a modified fall risk assessment tool (FRAT) within the EMR to assess outpatients at each infusion visit.[3] A "yes" response to any of the FRAT questions generates the application of a yellow fall risk wrist band and a yellow flag outside of the patient's room, similar to two of the bundle elements implemented at KUCC. In contrast to the quality improvement project results reported here, fall rates dropped from 5% to 0% within six months.[13]

Scant work has been conducted to qualitatively collect the experiences of healthcare team members regarding falls risk protocols and associated training, particularly in ambulatory oncology clinics. In the hospital setting, staff nurses may have the most influence in falls prevention.[13] Results from one recent hospital-based study indicated that intense falls prevention messaging from administration had a negative effect and led staff nurses to fear falls and to guard themselves against falls repercussions, such as job loss and public humiliation, resulting in nurses' desire to avoid caring for falls risk patients.[13] In our QI project, MAs had the most responsibility for falls prevention, and while present, the falls messaging did not serve to alarm the MAs or lead to job neglect. In contrast, MAs identified additional ways to help prevent falls in their clinic. One idea noted above from the MA interviews was to better educate patients on why falls prevention in the clinic was important. This idea is supported by results from a recent scoping review indicating that incorporating patient education into falls prevention strategies can reduce falls and accompanying injuries.[14] Patient education has been demonstrated to reduce falls in the hospital setting. A recent study was conducted to evaluate the impact of a fall prevention toolkit for patients and families in the hospital setting. Implementation of the toolkit was associated with a significant reduction in falls and concurrent injuries.[15]

This quality improvement project was restricted by several limitations. Utilization of the UKHS patient safety reporting system to describe KUCC fall rates and investigate pre/post bundle change was subject to the risk of under reporting inherent in adverse-event reporting systems dependent on self-report.[14,15] However, this system is the only available mechanism for collecting falls data at our institution. Another study limitation relates to the delay to initiate the qualitative interviews (from the Fall of 2020 to the Spring of 2021) due to staffing challenges related to the COVID-19 pandemic. Project Team members were deployed to meet direct care needs within the institution during this timeframe. These factors prolonged our data collection period for conducting the qualitative interviews and reduced the pool of MAs who were present for the original pre-bundle implementation education. Unfortunately, bundle development and implementation was

not customized by disease specialty and variability between individual outpatient clinics settings. No process procedures were put in place to monitor implementation compliance or satisfaction, nor were disease specialty stakeholders involved in the bundle development. A project strength was the important information gleaned from the qualitative interviews; however, the project design did not include methods to obtain insights from outpatient oncology patients or family members.

Project Teams' Recommendation. Results from the review of the data extracted from the institutional health systems' patient safety event reporting system provided evidence that dizziness, faintness, and weakness were the most cited descriptors associated with the fall incidents. Likewise, falls occurring during transfers commonly were noted. Taken together, along with the known association between postural hypotension and fall risk in primary care,[8,18] and the lack of an outpatient oncology clinic protocol for post infusion or procedure vital signs, the Project Team recommends development and implementation of an orthostatic vital sign protocol. The Project Team recommends that orthostatic vital signs be assessed prior to discharge for all high-risk patients, as well as following infusions and prone position procedures. Discharge should be delayed until blood pressure returns to baseline, or patients with documented postural hypotension whose family members are present should be escorted by wheelchair to their cars. Consideration also should be given regarding a policy for a discharge escort service for any patient deemed to be a high fall risk.

Review of the UKHS' patient safety event reporting system data also demonstrated lack of consistent or durable documentation of fall risk. The project team recommends a redesign of the EMR Falls Risk Banner so that this alert will be maintained for a six-month period following a fall or determination that a patient is a high fall risk. This recommendation was further supported by the results of the semi-structured qualitative interviews conducted with the MAs and nurse managers.

Development of a patient education strategy, such as an educational tool kit, with input from all stakeholders at our eight KUCC clinics is suggested. Longer-term solutions with budget ramifications are recommended for consideration by the cancer center leadership, such as safer chairs, adjustable exam tables, additional gait belts and wheelchairs, assistive devices, and bathroom redesign.

CONCLUSIONS

Results from this quality improvement project indicated that system-related policy and culture change, investment in physical and human resource enhancements, and evidence-based protocols are needed to improve outpatient oncology fall rates. Stakeholder involvement, multifactorial educational strategies, and unit-specific customization of ambulatory fall-risk protocols are desired by outpatient oncology clinic staff. The project findings were shared with cancer center leadership with priority assigned to the redesign of the EMR Falls Risk Banner functionality and implementation of the proposed orthostatic vital sign protocol for patients rated as high-risk on the fall risk assessment. Next steps include obtain input from all stakeholders, such as MAs, clinic RNs, nurse managers, patients/family members, and system administrators to redesign staff and patient education around mitigation of fall risks. The Project Team will continue to monitor and assess the incidence and type of falls as these recommendations are implemented.

Although this quality improvement project was conducted to identify and address outpatient oncology fall rates for one NCI-designated comprehensive cancer center, the lessons learned about the importance of stakeholder engagement in policy development are broadly applicable to other institutions.

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Keywords: clinic, outpatient; clinical oncology; falls, accidental; quality improvement

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The Effect of Bone Quality on Treatment of Intertrochanteric Fractures with Helical Blade Versus Lag Screw Fixation in Cephalomedullary Nails

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ABSTRACT

Introduction. The specific aim of this retrospective study was to determine whether bone quality has any effect on the complication rates or overall survivorship between helical blades and lag screws in cephalomedullary nails used for intertrochanteric hip fractures.

Methods. The authors reviewed clinical charts and radiographic studies of patients between January 2012 and August 2019. We reviewed radiographic images (pre-, intra-, and post-operative) to evaluate fracture fixation type, fracture reduction grade, and post-operative complications. We collected dual energy x-ray absorptiometry scan results (T-score) and serum alkaline phosphatase (ALP) isoenzyme activity values to evaluate patient bone quality.

Results. We included 303 cases (helical: 197, screw: 106) in the study. Complications were found in 31 (16%) helical blade cases and 23 (22%) lag screw cases. No statistically significant difference was detected when comparing complication rates with patient bone quality between the two groups. These two groups had similar one-year implant survivorship with respect to T-score, the low ALP level group, and normal ALP level group. The helical blade had higher implant survivorship compared to lag screw in five-year survival rate with respect to osteoporotic group, high ALP level group, and normal ALP level group (osteoporotic: 77% vs 69%, high ALP: 73% vs 67%, normal ALP: 70% vs 64%).

Conclusions. Similar complication rates were observed between helical blade and lag screw constructs in cephalomedullary femoral nails when accounting for patient bone quality. However, the helical blade design had a higher five-year survival rate. ***Kans J Med 2023;16:207-213***

INTRODUCTION

Intertrochanteric hip fractures are one of the most common injuries among the older adult population. They carry significant morbidity and mortality and have a large impact on quality of life.[1-4] The number of hip fractures treated each year is expected to continue to increase significantly,[5,6] and also is expected to substantially increase health care expenses.[4,6] Cephalomedullary nails have become the device of choice for fixation of unstable intertrochanteric hip fractures,[7-10] as these implants allow a fixed-angle construct, controlled fracture compression, and adequate stability for immediate post-operative weight bearing.[8,11] The cephalic screws are designed to be able to slide within the nail for compression while maintaining load-sharing characteristics at the fracture site. Currently, there are two main designs of cephalic screw implants available: helical blade (Figure 1A) and lag screw (Figure 1B). There are conflicting data in the literature when comparing these two cephalic screw designs.[12-17] Several studies have found no difference in the failure rate of trochanteric fractures treated with blade versus screw for femoral fixation.[12,16] Other studies have found that when the helical blade was used, implant cutout or implant migration occurred at a significantly higher rate compared with lag screw fixation.[13-15,17] Because of these conflicting data in the literature, many orthopedic surgeons select one screw design over the other for their patients based on their comfort level or personal experience. This illustrates the need for a better understanding of the advantages or disadvantages in the use of these two screw designs for intertrochanteric hip fractures as orthopedists aim to optimize patient outcomes.

As many intertrochanteric fractures are related to poor bone quality, it is important to consider the effect that bone quality may have on implant stability.[18,19] It is well known that accurate positioning of the cephalic screw in the femoral head affects the outcome following fixation of intertrochanteric hip fractures;[12,14,20,21] however, the role of bone mineral density (BMD) or alkaline phosphatase (ALP) levels has not been thoroughly evaluated. There are limited clinical studies in the literature that specifically examine the effect of BMD or ALP levels on the lag screw versus helical blade design for intertrochanteric hip fracture fixation. Most of the clinical studies to date have investigated the direct comparison between the blade and screw designs without considering the effect of bone quality.[10,13,14,16,21-23] To date, the majority of the literature pertaining to the effect of bone quality has been biomechanical or finite element modeling in nature.[15,17,24-27] Thus, the specific aim of this retrospective study was to determine whether bone quality has any effect on the complication rates or overall survivorship between helical blades and lag screws in cephalomedullary nails used for intertrochanteric hip fractures.

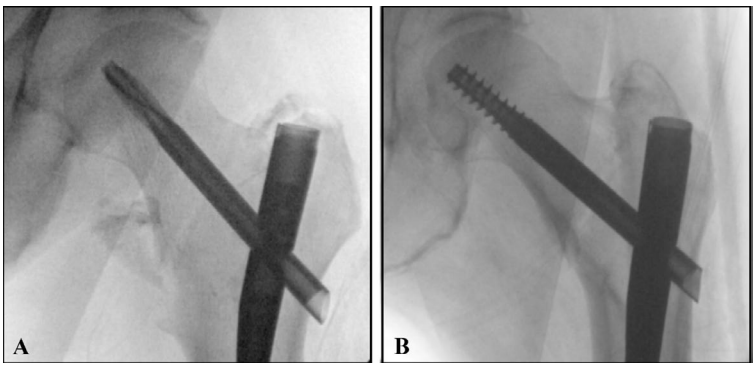

Figure 1. Cephalomedullary nails for unstable intertrochanteric hip fractures: (A) helical blade design, (B) sliding lag screw design.

METHODS

Participants. Approval for this study was obtained from our institute research committee and the institutional review board. The authors reviewed the clinical charts and radiographic studies of a consecutive series of patients (18 years and older) who had intertrochanteric fractures treated with a cephalomedulary nail. The inclusion criteria consisted of intertrochanteric hip fracture fixation procedures performed from January 2012 through August 2019 from designated Level-1 trauma centers within a single institution in the Midwestern Region of the United States. Patients with prior hip surgery, hip fractures other than intertrochanteric, hip fracture fixation not utilizing cephalomedulary nail, inadequate length of follow-up, or inadequate radiographs, including unavailable pre- or post-operative films, were excluded from the study. Patients with post-operative clinical and radiographic follow-up of less than three months were excluded from the study; however, patients with complication or failure within three months were included in the study. A minimum follow-up period of three months was similar to those described in the literature.[13,21,22,28,29] The surgical cases examined in this study included two commonly used cephalomedullary nails: the Stryker gamma nail (Gamma; Mahwah, NJ) and the Synthes trochanteric fixation nail (TFN; Paoli, PA). The cephalic screw fixation of these implants was performed with either a lag screw or a helical blade. The type of nail, as well as the decision to use a lag screw or helical blade, was made according to surgeon preference.

Variables. The retrospective chart review included information regarding patient age, gender, body mass index (BMI), surgical date, laterality of procedure, initial follow-up date, and latest follow-up date. The intra-operative or initial post-operative plain radiographic images of the hip, pelvis, or femur were utilized to determine the fixation type (lag screw or helical blade), hardware placement, and initial fracture reduction quality. A fracture reduction grade was scored for each case based on a modification of the criteria proposed by Baumgaertner, et al.[21] with Tip Apex Distance (TAD) measurement. The TAD measurements on the plain radiographic images were calibrated with the magnification error of the actual stem width. Fractures were graded as "good", "acceptable", or "poor" based on three radiographic criteria as judged on the radiographic images. These were (1) alignment on the anteroposterior (AP) film for anatomic or valgus alignment, (2) neutral alignment on the lateral film, and (3) absence of displacement > 4 mm on either view apart from a displaced lesser trochanter fragment. For a reduction to be considered "good", all three criteria were met. For an "acceptable" reduction, either alignment or displacement criteria were met, but not both. For a "poor" reduction, none of the three criteria were met.[21]

Bone quality or markers of bone mass assessment was performed using the dual energy x-ray absorptiometry (DEXA) scan results, and serum alkaline phosphatase (ALP) isoenzyme activity. The result of the DEXA scan is presented as a T-score, which represented the difference of the bone density from the average bone density of healthy young adults. The World Health Organization (WHO) operationally defines a T-score greater than -1.0 as normal, a T-score between -1.0 and -2.5 indicated low bone mass (osteopenia), and a T-score of -2.5 or less indicated osteoporotic.[30] The result of the ALP isoenzyme activity is presented as low, normal, and high levels. The normal range for the ALP blood test was defined as 44-147 international units per liter (IU/L),[31,32] low ALP level was defined as < 44 IU/L, and high ALP level as > 147 IU/L. High bone ALP levels may indicated have a type of bone disorder.[33,34]

Post-operative data collected included complication variables such as implant cut-out, implant migration without cut-out, femoral neck collapse, periprosthetic fracture, hardware failure or breakage, infection, and persistent hip pain. Survivorship in this study is defined as lack of complications or reoperation.

Statistical Analysis. Descriptive statistics were used to create demographic profile of the patients whose data were used in the study. Independent-samples student-t test with not assumed equal variances was used to evaluate for differences between groups by comparing population means and standard deviation of variables. For categorical variables, a one-sided Fisher's exact test analysis was used to determine statistical significance. The Pearson chi-square statistic was utilized to determine significant observed differences among bone quality (T-score and ALP) and post-operative comparisons related to bone quality. Frequencies and percentages for other variables were obtained. Kaplan-Meier survival analysis was performed to determine all-cause implant survivorship at final follow-up for every patient. This study assumed that (1) at any time the patients who were censored should have the same survival prospects as those who were still being followed in the study, (2) the survival probabilities were the same for patients recruited early and late in the study, and (3) the event happened at the time specified. Participants who have died are considered censored. All statistical testing methods used were performed using IBM SPSS Statistics software (Version 24.0; IBM Corporation, Armonk, New York), and statistically significant relationships were defined as those with p value of less than 0.05.

RESULTS

There were 303 intertrochanteric hip fracture cases (247 female, 56 male) identified, with 197 cases (159 female, 38 male) treated with helical blade and 106 cases (88 female, 18 male) treated with lag screw. The mean age was 77 years (SD = 9 years, range: 43 – 90 years) and the mean BMI was 26.1 kg/m^2 (SD = 6.5 kg/m^2, range: 15.0 – 54.6 kg/m^2). The mean follow-up period was 692 days (SD = 631 days, range: 19 – 2,993 days), and 52% (n = 157) were left hip injuries. There were no statistically significant differences in demographics between these two study groups (gender: p = 0.371; age: p = 0.858; BMI: p = 0.159; follow-up period: p = 0.480; site of procedure: p = 0.205).

Based on the DEXA scan results, most of the patients had either osteopenia (helical blade: 79 out of 197 patients [40%]; lag screw: 57 out of 106 patients [54%]) or osteoporosis (helical blade: 100 out of 197 patients [51%]; lag screw: 44 out of 106 patients [42%]) for both groups. However, there were higher numbers of osteoporosis patients (51%) in the helical blade fixation group, with higher numbers of osteopenia patients (54%) in the lag screw fixation group. There was no statistically significant difference detected between these two groups (p = 0.053).

Both groups had higher proportions of patients with normal ALP levels (helical blade: 71%; lag screw: 71%), and there was no statistically significant difference detected between these two groups (p = 0.252).

There were 31 out of 197 helical blade fixation cases (16%) and 23 out of 106 lag screw fixation cases (22%) that developed complications (Table 1). A lower rate of implant cut-out and persistent hip pain was observed in the helical blade group when compared to the lag screw group (cut-out: 4% vs 8%; pain: 3% vs 6%). Overall, there was no statistically significant difference detected between these two groups (p = 0.128). When comparing post-operative complication rates with respect to patient bone quality (T-score and ALP levels), there were no statistically significant differences detected between these two groups (Table 2).

Table 1. Complications for each group.

Complications	Helical blade (n = 31)	Lag screw (n = 23)
Implant cut-out	8 (4%)	8 (8%)
Device migration without cutout	2 (1%)	1 (1%)
Femoral neck collapse	3 (2%)	1 (1%)
Periprosthetic fracture	7 (4%)	5 (5%)
Hardware failure (bent)	3 (2%)	2 (2%)
Infection	2 (1%)	-
Persistent hip pain	6 (3%)	6 (6%)

Table 2. Post-operative complications evaluation results.

Variable		Helical blade (n = 31)	Lag screw (n = 23)	p value
Complication with T-Score	Osteopenia (-1 to -2.5)	14 (18%)	13 (23%)	0.301
	Normal (> -1)	4 (18%)	2 (40%)	0.392
	Osteoporosis (< -2.5)	13 (13%)	8 (18%)	0.284
Complication with ALP levels	Low (< 44 IU/L)	-	1 (33%)	0.600
	Normal (44 – 147 IU/L)	24 (17%)	19 (25%)	0.106
	High (> 147 IU/L)	6 (18%)	1 (8%)	0.402
	No data	1 (5%)	2 (13%)	0.396

When comparing implant survivorship with respect to T-score, the one-year survival rate for all four groups (osteoporotic, osteopenia, normal bone density, and all patients) between the helical blade design and lag screw design were similar (osteoporotic: 94% vs 92%, osteopenia: 89% vs 88%, normal: 76% vs 75%, and all patients: 90% vs 89%; Figure 2A vs Figure 2B). The five-year survival rate calculated by the Kaplan-Meier survival analysis for the osteoporosis group and all patients group in the helical blade design had higher survival rates compared to the lag screw design (osteoporotic: 77% vs 69%, all patients: 72% vs 62%); the survival rates were similar for the osteopenia group and normal bone density group between the two cephalic screw designs (osteopenia: 61% vs 63%, normal: 72% vs 75%; Figure 2A vs Figure 2B).

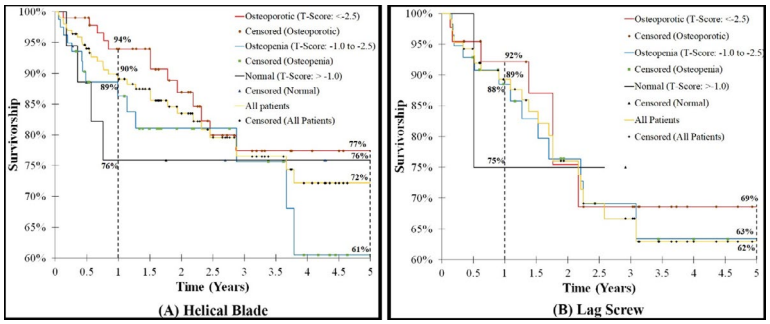

Figure 2. Survival analysis of unstable intertrochanteric hip fractures utilizing cephalomedullary nails related to T-score: (A) helical blade, (B) sliding lag screw design.

When comparing implant survivorship with respect to ALP levels, this study showed that the implant survivorship rate at mean follow-up of one year for the low ALP level group, normal ALP level group, and all patients group were similar between the helical blade design and lag screw design (low ALP level: 100% vs 100%, normal: 87% vs 87%, and all patients: 90% vs 89%). The high ALP level group had different survivorship rates between these two designs at mean follow-up of one year (94% [helical blade, Figure 3A] vs 100% [lag screw, Figure 3B]). The five-year survival rate for high ALP level group, normal ALP level group, and all patients group in the helical blade design had higher survival rates compared to the lag screw design (high ALP level: 73% [helical blade, Figure 3A] vs 67% [lag screw, Figure 3B], normal ALP level: 70% [helical blade, Figure 3A] vs 64% [lag screw, Figure 3B], and all patients: 72% [helical blade, Figure 3A] vs 63% [lag screw, Figure 3B]).

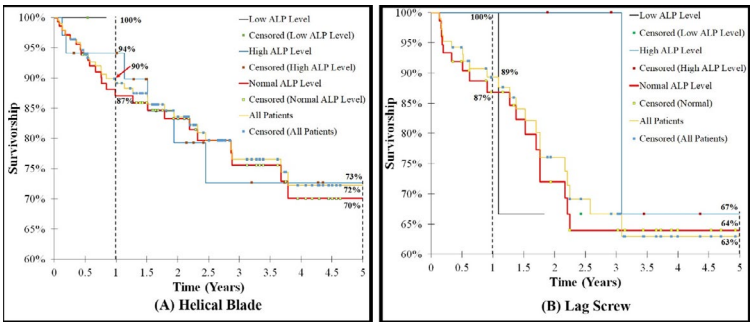

Figure 3. Survival analysis of unstable intertrochanteric hip fractures utilizing cephalomedullary nails related to ALP levels: (A) helical blade, (B) sliding lag screw.

When examining fracture reduction quality, most cases (n = 126) for the helical blade fixation group had good reduction quality, and 17 of those cases (13%) developed complications. Fifty-five out of 197 cases had acceptable reduction quality, and 11 of those cases (20%) developed complications. Sixteen out of 197 cases had poor reduction quality, and 3 (19%) of those cases developed complications (Table 3). In the lag screw fixation group, most cases (n = 68) had good reduction quality, and 10 (15%) of those cases developed complications. Ten out of 106 cases had poor reduction quality, and 4 (40%) of those cases developed complications (Table 4). Twenty-eight out of the 106 cases had acceptable fracture reduction, and 9 (32%) of those cases developed complications.

DISCUSSION

The primary aim of the present retrospective study was to examine the influence of bone quality on the complication rates and overall survivorship of intertrochanteric hip fractures treated with cephalomedullary nails using helical blades or lag screws for cephalic fixation. This study found a slightly lower complication rate in the helical blade group when compared to the lag screw group (16% vs 22%). Our data showed that lag screws and helical blades had equivalent performance with respect to T-score or ALP levels at one-year survivorship. However, five-year survival rates calculated with respect to T-score or ALP levels showed the helical blade design had a higher survival rate compared to the lag screw design.

Helical blades have been advertised as having theoretic advantages over lag screw fixation in the femoral neck component of cephalomedullary nails. They are designed to minimize bone loss during insertion and have greater rotational stability compared to lag screw fixation.[23] They also are theorized to have higher cutout resistance. However, the literature has been mixed regarding the veracity of these theories. A retrospective review by Chapman et al.[22] found a higher rate of failure when helical blades were compared to screws. They noted that helical blade failures tended to include more medial migration of the blade as opposed to the traditional superior implant cut out. However, a prospective randomized controlled study by Stern et al.[16] did not observe a significant difference in complication or cutout rates between helical blades and screws. We suspect that the discrepancy between these studies is caused by the different lengths of follow up. Chapman et al.[22] study had an average of 112 follow-up days (range: 94 - 125 days), whereas Stern et al.[16] study had a one-year follow-up. Prior studies have reported the follow-up period between 0.7 months and 74 months.[12-16,22] We did not observe an overall difference in complication rates between the two groups, and both helical blade and lag screw performed equally well at one-year follow-up; however, this study did note a greater five-year survivorship with helical blade design, especially for patients with osteoporosis. This suggests that helical blade implants may have a long-term advantage for patients with poor bone density. The results of this study suggest that most patients with normal T-score (> -1.0) can successfully be managed with either screw design, but those patients with true osteoporosis as diagnosed by DEXA scan may benefit from use of a helical blade design due to better implant survival in longer-term follow-up periods.

The use of the helical blades not only showed improved five-year survivorship compared to lag screws, but it also should be noted that when examining the subgroup of fractures with a "poor" reduction quality rating, helical blades demonstrated a lower complication rate than lag screws. When looking only at fractures with poor fracture reduction, we noted a 19% (3 out of 16 patients) complication rate in the helical blade group (Table 3) compared to a 40% (4 out of 10 patients) complication rate in the lag screw group (Table 4). Poorly reduced fractures were the minority in both groups; therefore, these numbers are not sufficient to reach statistical significance. However, this trend may suggest that the integrity of the lag screw fixation is more dependent on fracture reduction quality than the helical blade.

Femoral head bone quality is critically important for the integrity of the head screw component of cephalomedullary nails. The lag screw benefits from high-density bone in the femoral head to provide a sufficient gripping force.[35-37] On the contrary, the helical blade is designed to have increased purchase in the femoral head of patients with poor bone density. Unfortunately, there is no perfect method for assessment of bone quality of the femoral head. BMD of the hip is not constant and declines in the elderly population by approximately 0.5% per year.[38] In patients with a hip fracture, the hip BMD declines one year after the fracture ranges from 2% to 7%.[39,40] Karlsson et al.[39] investigated changes of BMD in 47 femoral neck fractures, and they concluded that osteoporotic hip fracture cases lose bone mass at an increased rate in the fractured hip relative to the uninjured hip. There was a BMD difference of 20–29% after 4 months and 1–6% after 12 months. Furthermore, BMD values vary among diabetic patients and can be increased, decreased, or remain normal.[41]

In patients with osteoporosis, the bone metabolism system is disordered, and the levels of bone metabolism markers such as ALP are abnormal. Biochemical markers of bone metabolism are affected by fractures, and total alkaline phosphatase (ALP) is considered one of the bone formation markers and has generally been considered a reliable indicator for evaluating bone structure and performance.[42] ALP exists on the cell membrane surface of osteoblasts,[43,44] which can inactivate the mineralization inhibitors pyrophosphate and osteopontin,[45] thus playing an important role in osteoid formation and mineralization.

Table 3. Bone quality, fracture reduction quality, and complications data in the helical blade design group.

T-score	ALP	All patients		Fracture reduction					
				Poor		Acceptable		Good	
		Cases (n=197)	Cx (n=31)	Cases (n=16)	Cx (n=3)	Cases (n=55)	Cx (n=11)	Cases (n=126)	Cx (n=17)
Normal (> -1.0)	Low*	-	-	-	-	-	-	3	-
	Normalβ	13	4	-	-	8	3	5	1
	Highδ	2	-	-	-	1	-	1	-
	No data	3	-	-	-	-	-	3	-
Osteopenia (-1.0 to -2.5)	Low*	-	-	-	-	-	-	-	-
	Normalβ	60	11	7	1	13	3	40	7
	Highδ	9	2	2	1	2	1	5	-
	No data	10	1	1	-	3	1	6	-
Osteoporosis (<-2.5)	Low*	2	-	-	-	2	-	-	-
	Normalβ	67	9	4	-	18	2	45	7
	Highδ	23	4	1	1	7	1	15	2
	No data	8	-	1	-	1	-	6	-

Note: Cx, Complications; *, ALP Level < 44 IU/L; β, ALP Level 44 – 147 IU/L; δ, ALP Level > 147 IU/L.

Table 4. Bone quality, fracture reduction quality, and complications data in the lag screw design group.

T-score	ALP	All patients		Fracture reduction					
				Poor		Acceptable		Good	
		Cases (n=106)	Cx (n=23)	Cases (n=10)	Cx (n=4)	Cases (n=28)	Cx (n=9)	Cases (n=68)	Cx (n=10)
Normal (> -1.0)	Low*	-	-	-	-	-	-	-	-
	Normalβ	3	1	1	-	1	1	1	-
	Highδ	1	-	1	-	-	-	-	-
	No data	1	1	1	1	-	-	-	-
Osteopenia (-1.0 to -2.5)	Low*	2	1	1	1	-	-	1	-
	Normalβ	42	10	1	-	11	4	30	6
	Highδ	5	1	1	-	-	-	4	1
	No data	8	1	2	1	1	-	5	-
Osteoporosis (<-2.5)	Low*	1	-	-	-	-	-	1	-
	Normalβ	30	8	1	1	12	4	17	3
	Highδ	6	-	1	-	3	-	2	-
	No data	7	-	-	-	-	-	7	-

Note: Cx, Complications; *, ALP Level < 44 IU/L; β, ALP Level 44 – 147 IU/L; δ, ALP Level > 147 IU/L.

Limitations. This study has certain limitations to recognize. First, a small sample size made it difficult to reach statistical significance on many variables. The low number of procedures included was unfortunately unavoidable due to a high rate of loss of follow-up secondary to patient mortality. Second, this study was a retrospective chart review study which introduces the possibility of selection and/or observation bias, as it was neither randomized nor blinded. Third, the patients who received cephalomedullary nails used for intertrochanteric hip fractures may have undergone revision surgery outside our institution post-operatively, which would not have been registered in this study, and subsequently falsely decrease the number of post-operative failures and other complications recorded. Furthermore, the changes of BMD, ALP, and other indices before and after surgery in the two groups were not recorded. Further evaluation in a larger randomized controlled study would be required to support the findings of this study.

CONCLUSIONS

In conclusion, the overall findings of this study showed bone quality had no influence on the complication rates between the helical blades and lag screws in cephalomedullary nails used for intertrochanteric hip fractures. Similar complication rates were observed between these two constructs; however, the helical blade design had a higher five-year survival rate.

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Keywords: hip fractures, intertrochanteric fractures, intramedullary nailing, helical blade screw, lag screw

KANSAS JOURNAL of MEDICINE

A Case of Persistent Postictal and Inter-ictal Delirium

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INTRODUCTION

Delirium is a sudden change in baseline brain function that causes a disturbance in attention, awareness, and memory that typically fluctuates in its course. Certain medications, infections, electrolyte abnormalities, and epileptic activity can trigger delirium.[1] Older adults and individuals with pre-existing neurological diseases are at an increased risk. Delirium is a challenging condition to manage and affects up to 50% of older hospitalized patients.[2] The clinical presentation includes abnormal changes in an individual's consciousness and thought processes and difficulty focusing and maintaining orientation.[3] Uncovering the inciting event and alleviating distressing symptoms are the focus of management. Initial evaluation includes laboratory blood and urine, and possibly cerebrospinal fluid testing, brain imaging, and electroencephalography (EEG).

While delirium typically improves over time, persistent delirium is associated with worse outcomes and increased morbidity and mortality.[4] Certain factors like sepsis, electrolyte abnormalities, and epileptic activity increase the likelihood of developing persistent symptoms of delirium.[5] A significant proportion of older adults with delirium were found to have epileptic activity and suggested the utility of continuous EEG in this population.[6] Additionally, immune-checkpoint inhibitor (ICI) therapies, such as pembrolizumab, are associated with the complication of neurotoxicity and the development of encephalitis.[7] Pembrolizumab works by binding to the protein PD-1 on the surface of certain cancer cells and is used to treat multiple cancers, including triple-negative breast cancer. The potential for pembrolizumab to induce a state of chronic epileptogenicity has been reported previously.[8] While neurotoxicity is a known complication of ICIs, there were limited data surrounding the occurrence of status epilepticus, the development of persistent delirium, and how to guide management.

In this case report, a 69-year-old female with a history of resected bifrontal meningioma and breast cancer treated with pembrolizumab presented with status epilepticus and subsequently developed persistent delirium. This case illustrated the multifactorial nature of persistent delirium and the contribution of prior brain dysfunction, pembrolizumab use, and infectious insults.

CASE REPORT

A 69-year-old female was transferred to the senior behavioral health unit (SBHU) for delirium after a prolonged admission to the neurocritical care unit (NCCU). Her history was significant for a resected olfactory groove skull base bifrontal meningioma, as shown in Figure 1, breast cancer in remission, and hypothyroidism. She received her most recent infusion of pembrolizumab for breast cancer adjuvant treatment two days before admission to the NCCU. In addition, psychiatric history was significant for the development of delirium-related visual hallucinations following surgical resection of the meningioma, and they were managed successfully with quetiapine. Before this admission, she lived with her husband and was independent in all her activities of daily living (ADLs). There was no report of prior seizures or family history of seizures.

Her initial presentation to the NCCU included altered mental status, an acute aphasia, and recurrent right facial twitching. Magnetic resonance imaging (MRI) brain showed chronic bifrontal encephalomalacia (Figure 1) secondary to the resection of her previous meningioma. However, no acute ischemia was seen on the MRI brain. Continuous video EEG subsequently was started and recorded left frontal status epilepticus (Figure 2). Seizures were treated with intravenous midazolam, levetiracetam, fosphenytoin, and valproic acid. Her course was complicated by septic shock in the setting of right lower lobe pneumonia, necessitating vasopressor support and mechanical ventilation for two weeks in the NCCU. She remained lethargic even after hemodynamic stability was achieved.

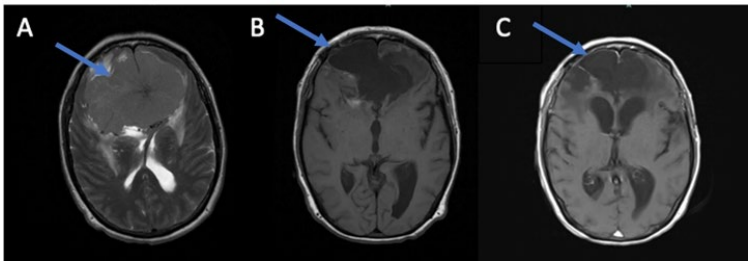

Figure 1. MRI showed: A) Large extra-axial mass centered in the anterior interhemispheric fissure exerting marked mass effect on the bilateral frontal lobes anteriorly and the anterior right temporal lobe. Mass was found to be a skull base meningioma and was subsequently resected. B) Postsurgical changes of mass resection from the anterior cranial fossa. No mass-like enhancement was seen to suggest residual tumor. Linear enhancement along the dura overlying the anterior left frontal lobe may represent continued postsurgical changes. C) Previous operative changes of frontal craniotomy with resection of a prior large interhemispheric meningioma. Postsurgical encephalomalacia, gliosis, and volume loss are unchanged from prior exam.

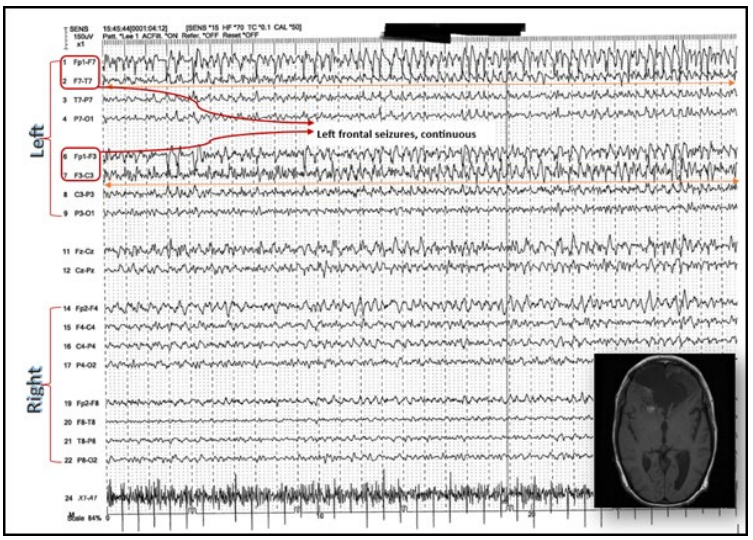

Figure 2. Excerpt of the first 30 seconds of continuous EEG recording. (Courtesy of Dr. Ricky Lee, neurology department at Via Christ St. Francis, Wichita).

Cerebral spinal fluid (CSF) evaluation was unrevealing. Due to concerns of oversedation, her antiepileptic regimen was tapered to include only levetiracetam 500 mg twice daily (BID) and lacosamide 200 mg BID. She became more alert and responsive and could follow simple commands and use a writing pad. However, following extubation, her course was complicated by the development of delirium with agitation and delusions, which prompted her transfer to senior behavioral health.

On admission to the SBHU, she remained confused in the setting of delirium; additional history was collected from medical records and collateral information provided by her husband. Initial examination revealed a frail elderly female alert and oriented to self, month, year, and location. Her remote memory was fair, and she was able to recount her past medical history. Her recent history was poor, and she did not know why she was hospitalized. She also perseverated on delusional beliefs surrounding the idea that her husband had been deceased for several years. She had leukocytosis with abundant immature neutrophils that were concerning for infection. However, no source could be identified, and the leukocytosis was resolved with empiric antibiotic treatment. Her clinical picture shifted from hyperactive delirium with agitation to hypoactive delirium with significant lethargy.

Treatment. During the hospital course, the patient failed three trials of antipsychotics, quetiapine, haloperidol, and risperidone; the last two agents were discontinued due to concern for decreased responsiveness and catatonic symptoms. Her antiepileptic regimen included initiation of lacosamide. She also failed the first trial of mirtazapine because of oversedation, but tolerated the second trial. Cognitive enhancer, memantine, was added, titrated to maximum daily dose with minimal benefits.

Outcome. Her mental status continued to fluctuate with minimal overall improvement. Further investigative studies were done over the course of her hospitalization, including blood cultures, cerebrospinal fluid analysis, meningitis/encephalitis panel, paraneoplastic antibody testing, cryptococcal antigen testing, HIV and syphilis antibody screens, and urinalysis. Following the resolution of sepsis, all studies were unrevealing for a cause of her persistent delirium. Repeat EEG evaluation demonstrated generalized background slowing without epileptogenic abnormalities.

Unfortunately, her delirium persisted over the next three months without significant improvement. She continued to need extensive nursing support regarding transferring, toileting, and feeding herself. Occasionally, she was alert and oriented to herself, location, and year, and she could hold short conversations before perseverating on a particular topic again. However, most days, she remained minimally interactive and oriented to herself, and her poor responsiveness rendered her unable to participate in the interview or exam. Figure 3 shows a timeline of this patient's assessment and treatment.

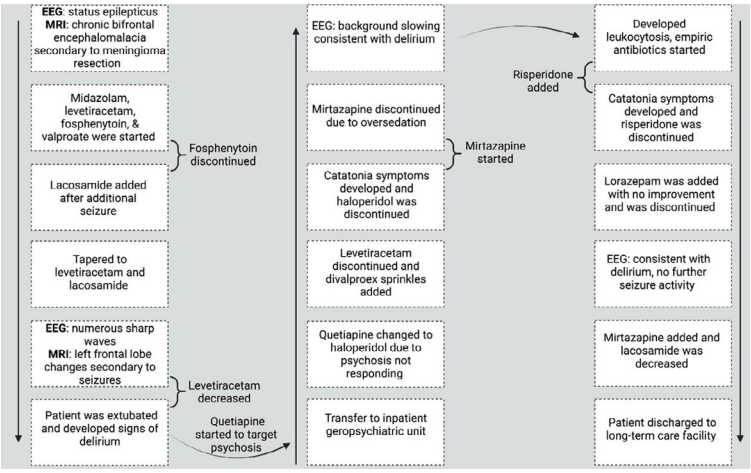

Figure 3. Timeline of patient's assessment and treatment. (Created with BioRender.com)

DISCUSSION

This case report illustrated the challenges of identifying definitive etiologies for persistent delirium, given the sophisticated interaction between various predisposing and precipitating factors, posing barriers to effective management, the need for which was highlighted by the high prevalence and increased morbidity and mortality. Indeed, 18 reports (involving 1,322 older hospital patients with delirium) compiled in a systematic review in 2009 suggested that persistent delirium at discharge, one, three, and six months comprised 44.7% (95% CI 26.8%, 63.7%), 32.8% (95% CI 18.4%, 47.2%), 25.6% (95% CI 7.9%, 43.4%) and 21% (95% CI 1.4%, 40.6%), respectively.[2] Additionally, more adverse outcomes, in terms of mortality, nursing placement, cognition and functional capacities, consistently were reported in persistent delirium.

One-third of 412 subjects with an average age of 84 and Mini-Mental State Examination (MMSE) of 12.5 from eight Boston area skilled nursing facilities specializing in post-acute delirious care had persistent delirium.[4] It was concluded that the cumulative one-year mortality was 39%, and there was 2.9% increase in one-year mortality in subjects with persistent delirium, when corrected for age, gender, comorbidity, functional status, and present of premorbid dementia. Notably, functional impairment leading to decreased ability to tend to Instrumental Activities of Daily Living (ADL) which is among the important prognostic indicators in persistent delirium.[4,9]

It was likely that in our case, the patient's prolonged delirious course rendered her fully dependent on ADLs in light of significant limitation with mobility and frailty, contributory to poor outcomes. Based upon her premorbid functioning, frailty appeared to be the sequela of persistent delirium and proved to be independent predictor of adverse outcomes. This was consistent with the findings of a 2018 prospective study which also revealed an inverse relationship between frailty and impacts of delirium on mortality.[10] In other words, delirium was found to have greatest implications in risk of death in fittest patients, likely explained by typically more serious insults for precipitation of delirium in patients with larger cognitive and physiological reserves. The study emphasized the presence of a distinct neurological determinant, harkening back to various neurological detriments our patient sustained, most prominently, history of bifrontal meningioma resection with encephalomalacia and status epilepticus.

A retrospective study investigating 177 patients with delirium identified 15% with epileptic activity on EEG, one-fifth comprising nonconvulsive status epilepticus.[6] Another prospective multicenter randomized controlled study revealed a 7% increase in prevalence of delirium in mechanically-ventilated patients with observable seizures and status epilepticus on EEG.[11] Both findings suggested a significant contribution of seizures to the evolution of delirium.[6,11] In another study, nonconvulsive status epilepticus and interictal discharges were found in 12% and 30% of elderly delirium patients, respectively, irrespective of the etiologies.[12] It can be theorized that the presence of an epileptic focus in the cortex promoted encephalopathy via widespread neuronal metabolism alteration, specifically in the functions of the cholinergic, serotonergic, and catecholaminergic systems in subcortical areas, which can produce diffuse cortical hypoactivity.[13] Both animal and human models demonstrated linkage between the affected and connected regions through synaptic changes, for which there is direct electrophysiological evidence via electrocorticography and motor mapping, which allowed visualization of changes induced by an intractable focal epileptic discharges.[13-15]

The clinical picture in our patient was obfuscated by the presence of sepsis secondary to pneumonia, as well as electrolyte (hypocalcemia and hypomagnesemia) and thyroid hormone abnormalities, all of which are well-known risk factors for seizures. Up to 20% of critically ill patients with sepsis developed seizures presented atypical in elderly populations.[5] The cytokine, IL-1β, creates an imbalance of N-methyl-D-aspartate (NMDA) and γ-amino-butyric-acid (GABA) activities, mediating calcium influx into neurons, synergizing with increased permeability of blood brain barrier for potentiation of neuronal excitability.[5,16]

Our patient highlighted the laborious process of elucidating the weights of relevant factors in persistent delirium. It was difficult to determine whether seizures caused encephalopathy or sepsis-associated encephalopathy predisposed the patient to epileptiform discharges in the backdrop of post-op structural changes. Additionally, there was a temporal relation between her pembrolizumab infusion and onset of seizures, and it was unclear whether pembrolizumab was culpable of unremitting epileptic activities.

The proposed pathophysiology is the induction of a chronic state of epileptogenicity similar to autoimmune epilepsy.[8] Regardless of morphologies, status epilepticus is associated with cerebral hypoxia, one of the aggravating factors in prolonged delirium.[9,17,18] The concomitant seizures in sepsis is a potential marker of brain dysfunction that has significant prognostic values.[6,18] Although the precise contribution of individual factors remains elusive, it a confluence was likely of all predictors for poor outcomes in our patient, not to mention the necessity of anticonvulsants that could exacerbate cognitive impairment. Levetiracetam might not be the ideal choice due to its implication in neuropsychiatric disturbances such as hallucinations, delusions, agitation with 13.8% of patients treated for focal epilepsy experienced psychiatric treatment-emergent adverse events, and that there was comparable efficacy of phenytoin, valproic acid, and levetiracetam in management of status epilepticus.[19,20]

In our case, cross-titration from levetiracetam to valproic acid saw improvement in psychiatric symptoms but no clinical change overall. According to the expert consensus guideline, valproic acid is considered for managing combativeness with high risk of physical aggression, further supporting the adjustment of her antiepileptic regimen, which our patient tolerated relatively well.[21] Her course of illness was compounded by the intolerability to antipsychotics, the benefits of which in delirium remain controversial, given the most severe or harmful adverse drug reactions were observed in 18% of patients in a systematic review of the literature regarding pharmacologic therapy for ICU delirium.[22] Haloperidol, a commonly used drug, did not show any clinical superiority over placebo, whereas quetiapine was found to have yielded faster resolution of delirium. Taking into account her previous quetiapine trial, it was possible that quetiapine could have precluded extrapyramidal effects and catatonic symptoms and engendered better outcomes. However, it remained questionable whether antipsychotics are recommended in the first place when delirium is linked to epileptic activity, and whether treatment strategies should be centered around anticonvulsant therapy.

Long-term cognitive impairment is one known repercussion of delirium, yet there was little research into the use of cognitive enhancers in such cases.[23] Memantine, an NMDA antagonist, is indicated to treatment of moderate-to-severe dementia of Alzheimer's type, and there was also evidence of significant efficacy in global functioning in vascular dementia with no difference in the number of people discontinuing memantine due to adverse effects.[24,25] Because there were available case reports of improvement in prolonged delirium with catatonia after memantine, our patient was trialed on memantine for cognition, while ensuring supplementation with folic acid and thiamine.[26,27] Unfortunately, in our patient, memantine proved to be of little clinical benefit; there had been minimal change until the patient was discharged to long term care.

CONCLUSIONS

The persistence of delirium, accompanied with profound morbidity and mortality, in its multifactorial nature, entail significant difficulties in prompt diagnosis and effective management. Sepsis and concurrent epileptic activity, specifically status epilepticus, are among poor prognostic markers, in which case, resolution of underlying etiologies did not translate into restoration of baseline cognitive and functional capacities. The efficacy of cognitive enhancers in prolonged delirium could be an area of active research. Further exploration into the overlap of symptoms between delirium and nonconvulsive status epilepticus could enhance understanding and help tackle this treatment conundrum.

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Keywords: delirium, seizures, encephalomalacia, meningioma

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Vaginal Delivery Following Thrombolytic Therapy in the Third Trimester: A Case Report

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INTRODUCTION

Stroke in pregnancy is a leading cause of maternal mortality, as it is estimated that 7.7-15% of all maternal deaths are due to stroke.[1] Risk factors for stroke in women include the prothrombic state of pregnancy and pregnancy-associated complications including preeclampsia and eclampsia.[2] Due to the commonly applied ethical barrier of including pregnant patients in randomized control trials, there are no clear guidelines for the management of pregnancy-associated stroke (PAS). Animal models suggest tissue plasminogen activator (tPA) does not cross the placenta, and a handful of case reports imply favorable outcomes with the use of tPA to treat ischemic infarcts in pregnancy.[3-6]

Despite the increased acceptance of tPA treatment in pregnancy, there remains a gap of knowledge pertaining to the timing of delivery in patients following tPA administration in the late third trimester. This is especially true in patients who have conditions in which immediate delivery is indicated, such as preeclampsia with severe features. The use of neuraxial anesthesia soon after tPA administration poses an additional clinical dilemma in which limited data exists. We present a patient with preeclampsia with severe features and persistent abnormal coagulation studies after tPA administration for presumed ischemic stroke who had an uncomplicated spontaneous vaginal delivery with epidural anesthesia.

CASE REPORT

A 31-year-old gravida 2 para 1 female at 36 weeks and 5 days by last menstrual period confirmed with ultrasound presented to the emergency department with acute onset left sided facial droop and left sided weakness. Past medical history was significant for preeclampsia in a prior pregnancy, sick sinus syndrome with single-lead pacemaker in place and prior ablations, anxiety, and depression. Her current medications included prenatal vitamin and 81 mg aspirin which she had not taken for two days prior to presentation.

Review of systems was unremarkable apart from left sided weakness and left sided facial droop. Vital signs were normal apart from a significant blood pressure of 144/79 mmHG. Subsequent blood pressure readings were within normal limits. Physical exam revealed left facial droop present in both upper and lower face with drift of the left arm and left leg with a National Health Institute stroke scale of 4. There were no sensory deficits. Laboratory values obtained were noncontributory and included a prothrombin time of 13 seconds, partial thromboplastin time of 23 seconds and an international normalized ratio of 1.0. Non-contrast head CT showed no intracranial abnormalities. 2D echocardiogram and carotid studies were unremarkable. At this time, her diagnosis was subradiographic stroke.

The patient received tissue plasminogen activator (tPA) two hours after symptom onset, after which her weakness and facial droop improved. She received 12 mg betamethasone four hours after symptom onset and magnesium 4-gram load followed by 1-gram per hour infusion. The patient was transferred to our tertiary care center and admitted to the neurology intensive care unit where she remained normotensive and afebrile. Given the patient did not have sustained elevated blood pressure readings, with the absence of proteinuria and any serum laboratory abnormalities consistent with preeclampsia, the managing teams felt she did not have preeclampsia and continued expectant management without magnesium sulfate infusion. She was subsequently transferred to the labor and delivery unit for further maternal and fetal monitoring.

Two days after symptom onset, pertinent labs included a hemoglobin of 11.1 gm/dL, platelet count of 204,000 K/uL, AST of 15 u/L, ALT of 17 u/L and 24-hour urine protein of 323 mg. Her aspirin dose had been increased to 325 mg daily, and on hospital day three she started to have sustained mild-range blood pressure readings. She was diagnosed with preeclampsia with severe features based on elevated blood pressure with neurologic changes. Magnesium sulfate was reinitiated with 4-gram bolus followed by 2-gram per hour continuous infusion. Given the patient's history of sick sinus syndrome, a 4-gram magnesium load was opted over a 6-gram load to avoid potential arrythmias. Additionally, the patient had a normal body mass index, an indication that she would be likely to reach therapeutic magnesium levels at a 4-gram load dose. Coagulation studies 48 hours after symptom onset included a PT of 10.4 seconds, PTT of 22.1 seconds, international normalized ratio of 0.9 and a critically low fibrinogen of 82 mg/dL. Thromboelastogram revealed low MA Kaolin at 45.5 (normal > 49.9 MM), reflecting low clot strength, and mildly elevated Lysis30 at 11.1 (normal less than 8.1%), increasing concern for fibrinolysis. A noncontrast MRI head revealed no intracranial abnormalities and a noncontrast head MRV showed no evidence of sinus venous thrombosis. The possibility of Bell's palsy was considered but unlikely due to concomitant limb involvement.

After extensive risk stratification between the threats of preeclampsia with severe features versus induction of labor with high hemorrhage risk, particularly from a critically low fibrinogen level, the multidisciplinary consensus was to follow fibrinogen levels for 24 hours to further assess hemorrhage risk prior to delivery. Had coagulation studies been normal, induction of labor would have been indicated for the patient given her diagnosis of preeclampsia with severe features. The option for Cesarean delivery under general anesthetic was considered too high risk for further neurologic injury. The patient was well informed on the potential risks of neuraxial anesthesia after tPA and remained decisive on an epidural for labor, even if transfusion would be required to obtain one.

In the next 12, 24, and 36 hours, the patient's fibrinogen levels increased to 111 dL/mg, 132 dL/mg, and 131 dL/mg, respectively. Her left sided weakness and facial droop continued to improve throughout this time. On hospital day five, five units of cryoprecipitate and one pack of single donor platelets were transfused and repeat thromboelastogram was normal. Neuraxial anesthesia was placed

immediately after transfusions and labor was induced with oxytocin. Seven hours after transfusions and induction, the patient's fibrinogen was 155 mg/dL. The patient delivered a healthy female infant at 37 weeks and 2 days gestational age 12 hours after induction without complications. Apgar scores at 1 and 5 minutes after delivery were 9 and 9. Venous and arterial cord blood gases were both within normal limits at 7.42 and 7.28, respectively. Additionally, there was no neonatal hemorrhage. Magnesium infusion was continued for 24 hours after delivery.

The patient's fibrinogen level eight hours after delivery was 195 mg/dL. After extensive discussion between our blood bank pathologist and OB anesthesiologist, we transfused another five units of cryoprecipitate, and the epidural was removed without issue. Coagulation labs continued to normalize. The patient was discharged on postpartum day three after a normal repeat CT head and neck. She had met all discharge criteria and instructed to follow up in six weeks.

DISCUSSION

Pregnancy-associated stroke (PAS) is projected to occur at a 3-to-13-fold increase in pregnant people compared to non-pregnant, and evidence suggests the incidence is increasing.[7] For non-pregnant patients, thrombolytic therapy with tPA for ischemic stroke, pulmonary embolism, or myocardial infarction is an acceptable therapy.[8] Despite the increasing acceptance of thrombolytic therapy in pregnancy-associated infarcts, there lacks sufficient data from randomized controlled trials for the use of tPA in pregnancy and a knowledge gap remains for optimizing delivery timing to best reduce risk of hemorrhage.[4-6] Specifically, there are minimal reports discussing the management of third-trimester patients who are treated with tPA that results in prolonged abnormal coagulation studies.

The current guidelines for management of preeclampsia with severe features is to deliver at 34 weeks gestational age if there is no prior indication for delivery.[9] The management becomes unclear when coagulation studies are critically abnormal and postpartum hemorrhage risk is high. The case presented provides a strong example of appropriate timing of delivery for patients with newly diagnosed preeclampsia with severe features when also needing to balance the risk of postpartum hemorrhage. Management becomes even more complex in patients who desire delivery with neuraxial anesthesia, which poses an additional risk of hemorrhage and spinal hematoma.[8] It is estimated that 60% of women chose epidural or combined spinal anesthesia during labor and delivery.[9] There are currently different management guidelines for different types of anticoagulant and antiplatelet therapy, but it is overall accepted that coagulation studies should normalize prior to neuraxial anesthesia.[10] This complicates management plans for patients who desire a vaginal delivery with neuraxial anesthesia who also have critically abnormal coagulation studies.

While the use of thrombolytics to treat ischemic embolisms in pregnancy is becoming more accepted, there is limited research on the risks and benefits of neuraxial anesthesia after thrombolytic therapy. Because of the large percentage of women choosing neuraxial anesthesia during labor and the increase in ischemic embolism during pregnancy, there is a need for research regarding the management of pregnant patients who received thrombolytic therapy.

CONCLUSIONS

There are no clear management guidelines for pregnancy-associated stroke when delivery is indicated due to other risk factors like preeclampsia with severe features. Decisions regarding type of anesthesia and mode of delivery are complex. Risks of performing general anesthesia shortly after a pregnancy-associated stroke need to be weighed against the risks of expectant management and risks of neuraxial anesthesia after treatments like tPA. The case presented is an example of a complex patient with preeclampsia with severe features who underwent an uncomplicated spontaneous vaginal delivery with regional anesthesia after tPA administration. We highlight how additional research is needed to establish clear guidelines on the management of stroke in pregnancy with subsequent abnormal coagulation studies.

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KANSAS JOURNAL of MEDICINE

Non-HIV Kaposi Sarcoma in an Immunocompetent Patient with High-Risk Behavior: Elucidating Subtypes and Risk Factors for Diagnosis

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INTRODUCTION

Kaposi sarcoma (KS) is a rare type of cancer that affects the blood vessels and can present as skin, mucous membrane, or internal organ lesions. It commonly is associated with human immunodeficiency virus (HIV) infection but also can occur in non-HIV infected individuals, especially in those with a history of immunosuppressive therapy, organ transplantation, or chronic lymphedema.[1] Although rare, classic Kaposi sarcoma can present in an individual with no known history of immunosuppression.[2] The diagnosis of KS in non-HIV infected individuals often is delayed due to a lower index of suspicion, which can lead to poor outcomes. Therefore, it is crucial to consider Kaposi sarcoma in the differential diagnosis of patients with suspicious skin lesions, regardless of their risk factors for the disease.[1]

There has been an observed rise in non-HIV-related Kaposi sarcoma cases in the context of declining HIV-associated cases attributed to the success of antiretroviral therapy (ART), as there has been a 75-90% decrease in incidence since the introduction to ART.[3] This has been juxtaposed by non-HIV-related Kaposi sarcoma which has increased from 12.4% to 37.1% between 1991 and 2013, respectively.[4]

Early recognition and diagnosis of KS can lead to prompt treatment and improved outcomes; this is crucial considering one of the best predictors for prognosis is early treatment.[5] KS can present with a wide range of clinical manifestations and may be mistaken for other conditions, such as ecchymoses, hematomas, or purpura. Historically, when these signs occur in an HIV-infected patient, KS is many times the leading differential. However, with the increasing incidence of non-HIV KS cases, there has been a clinical shift to considering KS in non-HIV patients who present with suspicious skin lesions, especially those who have a history of immunocompromised state.[1]

This case report highlights a rare presentation of non-HIV related KS in a high-risk immunocompetent patient and emphasizes the importance of early recognition and accurate diagnosis of this unusual form of the disease in all patients with suspicious skin lesions, regardless of known history of immunosuppression. It is important to increase awareness among clinicians of the importance of considering non-HIV KS in their differential diagnosis when evaluating patients with suspicious skin lesions.

CASE REPORT

A 64-year-old male with diabetes (recent hemoglobin A1c 6.9%), hypogonadism, actinic keratosis, previous history of basal cell carcinoma (definitively treated surgically), previous history of squamous cell carcinoma (definitively treated surgically), and high-risk men-who-have-sex-with-men behavior presented to the clinic for concerns of two, solitary purple growths on his left forearm and left upper arm. He reported that the lesions were new to him, nonpainful, nonpruritic, and had some mild-moderate bleeding. He noted that nothing made them better or worse and have been present for three weeks. His family history was remarkable for non-melanoma skin cancer. He was on metformin, testosterone gel, and Emtricitabine-Tenofovir.

Physical examination was unremarkable except for integumentary lesions. He had purple, pearly, and telangiectatic papules noted on his upper left arm and left forearm (Figure 1). Additionally, he had non-hyperkeratotic, erythematous scaly papules distributed on his ears, face, and trunk which were diagnosed as actinic keratoses by his dermatologist.

Laboratory workup was negative for HIV-1/HIV-2 antibodies, HIV-1 p24 antigen, Chlamydia trachomatis, and Neisseria gonorrhoeae. Further lab results were all normal (Table 1): CD4 count 704 (359-1519 /uL), IgG 938 (603-1613 mg/dL), IgA 364 (61-437 mg/dL), IgM 92 (20-172 mg/dL), and IL-6 3.1 (0.0-13.0 pg/mL). He was positive for Treponema pallidum antibodies and RPR was reactive with a 1:1 quantity.

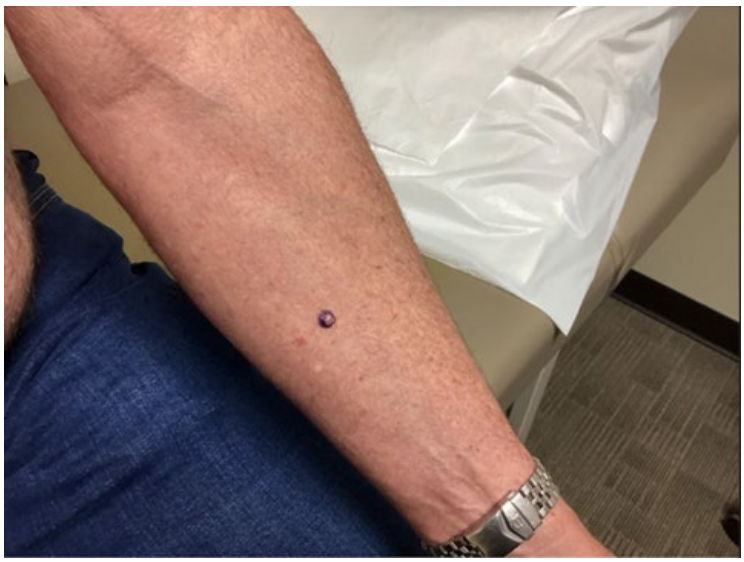

Figure 1. Purple, pearly telangiectatic lesion noted on patient's left forearm.

The lesions were excised, and the specimens were sent for a pathology report. The report revealed that the specimen showed a relatively circumscribed, but unencapsulated intradermal spindle cell neoplasm consisting of fascicles of quite uniform spindle cells with palely eosinophilic cytoplasm. Immunostains showed diffuse positivity for CD34, ERG, and HHV8. The findings suggested the diagnosis of nodular KS. With the confirmed history of no HIV, the diagnosis of non-HIV KS was confirmed.

Table 1. Relevant lab values.

Relevant laboratory tests	Lab values	Normal ranges
HIV-1/HIV-2 antibody	Negative	
HIV-1 p24 antigen	Negative	
Chlamydia trachomatis antibody	Negative	
Neisseria gonorrhoeae antibody	Negative	
Treponema pallidum antibody	Positive	
Rapid Plasma Reagin	Reactive: 1:1	
CD4 count	704/uL	359-1519/uL
IgG	938 mg/dL	603-1613 mg/dL
IgA	364 mg/dL	61-437 mg/dL
IgM	92 mg/dL	20-172 mg/dL
IL-6	3.1 pg/mL	0.0-13.0 pg/mL

DISCUSSION

KS is a rare, multifocal, angioproliferative neoplasm characterized by the development of lesions on the skin, mucous membranes, and occasionally internal organs. The patient was at risk for exposure to a wide range of infectious diseases that complicated the diagnostic process. This difficulty further demonstrates the need to understand all subtypes and risk factors of KS to make accurate diagnosis and choose appropriate management of KS.

There are four distinct clinical subtypes of KS, namely classic Kaposi sarcoma (CKS), endemic African Kaposi sarcoma (EAKS), iatrogenic Kaposi sarcoma (IKS), and epidemic Kaposi sarcoma or HIV-associated Kaposi sarcoma (HIV-KS).[1] The exact cause of KS is not fully understood, but it is thought to be caused by the human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV). HHV-8 is found in all types of KS and is necessary for the development of cancer.[6] Understanding all subtypes of Kaposi sarcomas is crucial in providing accurate diagnosis and appropriate management.

CKS predominantly affects elderly men of Mediterranean, Eastern European, or Middle Eastern descent, presenting with indolent, slow-growing cutaneous lesions that primarily involve the lower extremities.[7] It is the least aggressive form of KS, with the lesions generally not progressing to visceral involvement.[1]

EAKS occurs in individuals residing in sub-Saharan Africa, presenting a more aggressive course than CKS. EAKS affects both children and adults, with the pediatric form being particularly aggressive and rapidly progressing to visceral involvement.[8]

IKS is associated with immunosuppression following organ transplantation. IKS typically develops within one to two years after transplantation, often presenting with cutaneous lesions similar to CKS. However, these lesions may rapidly progress to visceral involvement, especially in cases of insufficient immunosuppression reduction.[9]

HIV-KS is the most aggressive form and has become the most prevalent subtype due to the global HIV/AIDS pandemic. HIV-KS primarily affects men who have sex with men and is characterized by rapidly progressing cutaneous and visceral lesions.[10] It is important to maintain a broad diagnosis for diseases, even if the presenting disease does not fall in line with typical co-presenting symptoms or comorbidities.

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KANSAS JOURNAL of MEDICINE

A Scoping Review to Assess Risk of Fracture Associated with Anxiolytic Medications

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ABSTRACT

Introduction. Recent research has focused on evaluating the impact of pharmalogical sources on fracture risk. The purpose of this study was to review the literature on anxiolytic medications that may be associated with an increased risk of fracture.

Methods. A search was conducted in MEDLINE and Embase databases to identify primary clinical studies of patients who sustained a fracture while prescribed anxiolytic medications and were published prior to July 2021. Anxiolytics defined by ATC Class N05B, beta blockers, and zolpidem were included. The search terms consisted of variations of the following: ("Psychotropic Drugs" or MeSH terms) AND ("Fracture" or MeSH terms).

Results. Of 3,213 studies, 13 (0.4%) met inclusion criteria and were evaluated. Fractures associated with benzodiazepine were reported in 12 of 13 studies; the highest risk occurred in patients aged 60 years and older (RR=2.29, 95% CI (1.48-4.40)). The ATC Class N05B showed an increased fracture risk for those ≤ 55 years of age that differed by sex: for men (RR=5.42, 95% CI(4.86-6.05)) and for women (RR=3.33, 95% CI (3.03-3.66)). Zolpidem also showed an increase fracture risk (RR=2.29, 95% CI(1.48-3.56)), but only during the first four weeks of treatment. A relative risk of 0.77, 95% CI(0.72-0.83) was observed for beta blockers.

Conclusions. Fractures are a mainstay of traumatic injuries and are accompanied by economical, physiological, and psychological hardship. With proper assessment and prophylactic measures, fracture risk can be reduced dramatically. Anxiolytic medications have been described widely to increase fracture risk, such as benzodiazepines in 60+ year old patients, and ATC Class N05B anxiolytics increased fracture risk in 55+ year old men and in 55+ year old women. Yet, some studies showed that at low doses, nitrazepam lowered fracture risk. Other anxiolytic medications, such as zolpidem and beta blockers, also showed a decrease in fracture risk. Ultimately, this scoping review helped to illuminate the inconsistency of anxiolytic fracture risk assessment while simultaneously illustrating the necessary steps to guide future research.

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INTRODUCTION

Fractures have a significant impact on physical and psychological function, independence, quality of life, and mortality, and may cause devastating economic consequences for patients and their families.[1-6] In 2021, Blankart, et al.[7] estimated end of life hip fracture patients experienced a hospital stay expenditure of $22,508, which did not include emergency department costs, specialist spending, primary care charges, and pharmacotherapy payments. Ultimately, fractures are expensive events that occasionally can be prevented with assessment of a patient's risk for fracture, counseling, and initiation of appropriate preventative measures. Researchers have began identifying pharmalogical sources that increase fracture risk. In the psychotropic arena, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and antipsychotics have been associated with an elevated fracture risk;[8-10] however, the fracture risk of anxiolytics has been evaluated less than other classes of psychotropic medications.

The class of anxiolytics consists of Z-drugs (zopiclone, eszopiclone, zaleplon, and zolpidem) beta-blockers, and members of the World Health Organization's ATC Class N05B (benzodiazepines, diphenylmethanes, carbamates, dibenzo-bicyclo-octadienes, and azaspirodecanediones).[11,12] In this review, some articles discussed benzodiazepines separate from the entire ATC Class N05B anxiolytics. All members in the class of anxiolytics are utilized to mitigate anxiety-provoking stimuli, but the pharmacologic effects could be accompanied by side effects such as blood pressure fluctuations, cognitive impairment, and delirium, which can lead to falls.[13-15] In the geriatric population, falls cause 95% of hip fractures which may result in decreased long term mobility and nursing home admission.[16] While some psychotrophic medications have been associated with an increased risk of fracture, anxiolytics, which are prescribed more commonly, have not been evaluated systematically. This is unfortunate as research shows an increase in the lifetime prevalence of hospital diagnosed anxiety, anxiolytic drug prescriptions, and self-reported anxiety were 4.4%, 6.2%, and 5.1%, respectively.[17]

Moreover, the prevalence of anxiety may have increased substantially due to the COVID-19 pandemic. Thus, there was a critical need to evaluate and identify anxiolytic medications that may be increasing the risks of fractures in individuals. The purpose of this study was to review the literature on anxiolytic medications and ascertain their association with increased fracture risks.

METHODS

Literature Search. This review utilized the Preferred Reporting Items for Scoping Reviews and Meta-Analyses (PRISMA-ScR)[18] guidelines. Approval from our institutional review board was not required. A research focused, university librarian assisted in the development of the search strategy to identify eligible studies (Appendix 1; appendix is only available online at journals.ku.edu/kjm). A search was conducted of MEDLINE and Embase in July 2021, using the following search terms: ("psychotropic drugs" OR related MESH terms) AND ("fracture" OR related MESH terms). These terms included anti-anxiety agents, anxiolytics, anxiety, medication (benzodiazepine, alprazolam, anthramycin, bromazepam, clonazepam, devazepide, diazepam, flumazenil, flunitrazepam, flurazepam, lorazepam, nitrazepam, oxazepam, pirenzepine, prazepam, temazepam, chlordiazepoxide, clobazam, clorazepate dipotassium, estazolam, medazepam, midazolam, olanzapine,

triazolam), accidental fall, accident, road accident, fracture, and adult. See Appendix 2 for exact search strategy for each database and MESH terms (appendix is only available online at journals.ku.edu/kjm).

Study Eligibility. Inclusion criteria consisted of articles with the following description: English language, human studies, anxiolytic medication use, and fracture risk assessment. Studies with level I-IV evidence were considered for inclusion. Animal, cadaver, duplicate studies found between databases, fractures not associated with anxiolytic medications, expert opinion, and review articles were excluded.

Study Selection and Data Abstraction. All studies were gathered initially by a research focused university librarian. Two researchers independently screened articles based on title, followed by an additional round of screening based on abstracts. If disagreement upon gathered articles occurred, a third member of the research team was consulted. Next, the same two researchers reviewed the full articles and gathered data. No automated tools were implemented in the screening process. Data collection included name of medication, number of patients, number of each sex, age range, mean age, follow-up or length of time to event, and fracture risk. Other data that was extracted included a description of the study and the level of the study. When applicable, reported outcomes were converted to risk ratios according to chapter six in Cochrane's Handbook.[19] A risk of bias assessment for non-randomized studies of interventions was conducted using ROBINS-I.[20]

RESULTS

For the initial literature search, 3,213 articles were identified, of which 0.4 % (13 out of 3,213) met inclusion criteria (Figure 1). Table 1 summarizes the included studies: 76.9% (10/13) were retrospective cohorts, with 92.3% (12/13) level III evidence. Length of time to fracture was not discussed in 46% (6/13) of studies; for the remainder, there were substantial variations regarding timeframe that included, 14 to 180 days. Regarding participant demographics, 38.5% (5/13) did not identify sex, and age ranged from 18 to 60+ years. Table 2 shows results of the bias assessment using ROBINS-I.

Of the medications analyzed, benzodiazepines (labeled as benzodiazepines, specific benzodiazepine, or anxiolytics) were the focus in 92.3% (12/13) of the studies, while ATC Class N05B anxiolytics, beta blockers, and zolpidem were investigated in 38.5% (5/13), 7.7% (1/13), and 7.7% (1/13), respectively. The majority of studies analyzing risk of fracture with benzodiazepine appeared to report increased risk of fracture; however, results were inconclusive. For example, a potential benefit was reported for a low dose of nitrazepam (OR=0.4, 95% CI (0.1, 2.9)), though results were not statistically significant.[26] Conversely, a significant increased risk was reported in a case control study of 60+ year old patients (RR=2.29, 95% CI (1.48-4.40)).[25] Moreover, studies with oxazepam and lorazepam[26] reported wide confidence intervals (95% CI (0.5, 57.2), which merit further investigation. Important details of drug regimen were not reported consistently, and these findings

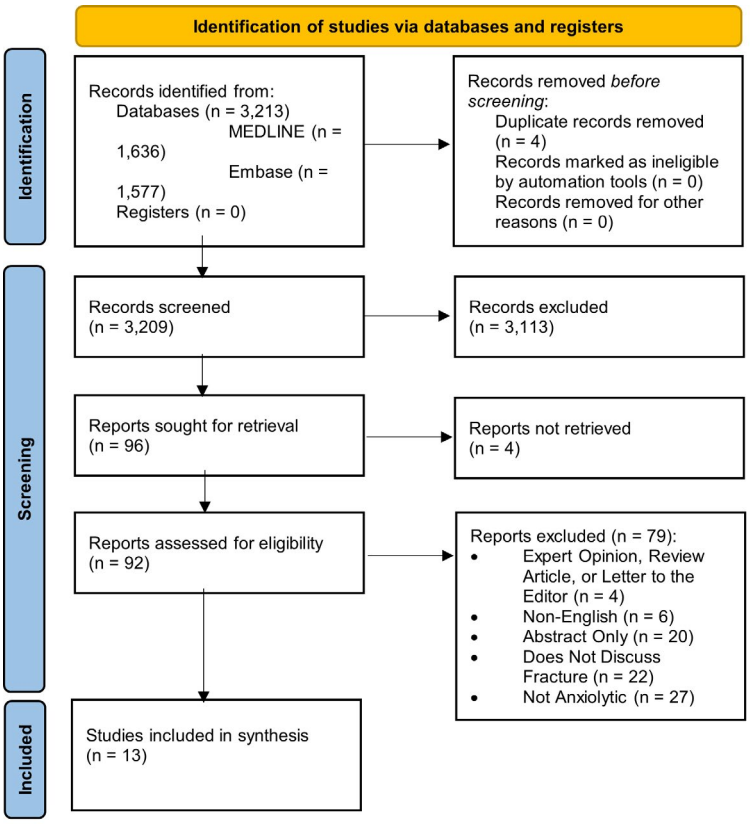

Figure 1. Identification of studies.

may be confounded by dosage. Last, a statistically significant increased risk for fracture was observed across multiple cultures and geographically diverse populations such as those in Spain (RR=1.18, 95% CI (1.07-1.30)), Denmark and the Netherlands (RR=2.20, 95% CI (1.33-3.61)), and the United Kingdom (RR=1.71, 95% CI (1.53-1.91)).[28]

Though ATC Class N05B were not studied as frequently, all reported significant increased fracture risk, for example, in men (RR=5.42, 95% CI (4.86-6.05)) 55+ years of age, but less for women (RR=3.33, 95% CI (3.03-3.66)).[22] Beta blockers were evaluated from one study; results showed a reduced risk of fracture (RR=0.77, 95% CI (0.72-0.83)), and remained beneficial across age groups and sex.[29] Zolpidem, when first started (0-4 weeks), showed a statistically significant increase for fracture risk (RR=2.29, 95% CI (1.48-3.56)).[27] Results for later times were inconclusive. As for beta blockers, the only study showed a statistically significant decrease in fracture risk regardless of patient's age or sex.[29] Overall, depending on study design, specific medication, age, and sex, fracture risk associated with anxiolytic drugs fluctuated greatly.

Table 1. Medications investigated as well as their respective fracture rate for each study analyzed.

	Year of publication	Level of study	Study description	Total participants	Females	Age range (years)	Length of time to fracture	Medication	Fracture risk
Abrahamsen et al.[21]	2009	3	Retrospective Cohort	Not Provided	Not Provided	50+	Not Provided	Anxiolytics*	PAR = ~2% any fracture risk PAR = ~2% hip fracture risk
Axmon et al.[22]	2018	3	Retrospective Cohort	7,936	3,609	55+	Not Provided	Anxiolytics*	Men: RR = 5.42 (4.86-6.05) Women: RR = 3.33 (3.03-3.66)
Bakken et al.[23]	2014	2	Prospective Cohort	2,009	1,642	60+	Patient must have been on drug for at least 14 days.	Anxiolytics*	Men: RR = 1.6 (1.4-1.7) Women: RR = 1.4 (1.4-1.5)
								Short-Acting Benzodiazepines	Men: RR = 1.7 (1.5-2.0) Women: RR = 1.4 (1.3-1.5)
								Long-Acting Benzodiazepines	Men: RR = 1.3 (1.2-1.5) Women: RR = 1.2 (1.2-1.3)
Bushnell et al.[24]	2020	3	Retrospective Cohort	57,684	37,848	18 to 24	Patients initiating anxiolytic therapy were followed until fracture, discontinuation or switching, disenrollment, 3 months, or study ended.	Benzodiazepines	Incident Rate Ratio: 1.02 (0.86-1.21)
Coutinho et al.[25]	2008	3	Case Control	500	110	60+	Not Provided	Benzodiazepines	RR = 2.29 (1.48-4.40)
Herings et al.[26]	1995	3	Retrospective Cohort	493		55+	A dispensing history of at least a 180 day is required.	Benzodiazepines	Overall RR = 1.44 (1.16-1.75)
								Nitrazepam**	Low Dose: OR = 0.4 (0.1-2.9) High Dose: OR = 1.1 (0.7-1.8)
								Oxazepam**	Low Dose: OR = 0.8 (0.4-1.5) High Dose: OR = 5.1 (0.5-57.2)
								Lorazepam**	Low Dose: OR = 5.1 (1.2-22.2) High Dose: OR = 5.5 (1.3-23.1)
								Temazepam**	Low Dose: OR = 1.0 (0.5-2.1) High Dose: OR = 2.8 (1.3-5.8)
Hwang et al.[27]	2015	3	Retrospective Cohort	6,623	3,562	18+	0-4 week exposure period 4-8 week exposure period 8-12 week exposure period 12-16 week exposure period	Benzodiazepines	0-4 weeks: RR = 1.46 (1.28-1.66) 4-8 weeks: RR = 1.23 (1.01-1.49) 8-12 weeks: RR = 1.09 (0.86-1.37) 12-16 weeks: RR = 1.38 (1.07-1.77)
								Zolpidem	0-4 weeks: RR = 2.29 (1.48-3.56) 4-8 weeks: RR = 1.90 (0.93-3.89) 8-12 weeks: RR = 2.33 (0.92-5.93) 12-16 weeks: RR = 1.83 (0.72-4.64)
Requena et al.[28]	2016	3	Retrospective Cohort	Spain 894: - 418,896 person years UK 436: - 129,857 person-years Netherlands & Denmark 20: - 8,022 person-years	Not Provided	18+	An exposure of at least 30 days is required.	Benzodiazepines	Spain: RR = 1.18 (1.07-1.30 United Kingdom: RR = 1.71 (1.53-1.91) Netherlands and Denmark: RR = 2.20 (1.33-3.61)

Table 1. Medications investigated as well as their respective fracture rate for each study analyzed. *continued.*

	Year of publication	Level of study	Study description	Total participants	Females	Age range (years)	Length of time to fracture	Medication	Fracture risk
Schlienger et al.[29]	2004	3	Case Control	932	640	30+	Last prescription had to be filled 1-59 filled days prior.	Beta-Blockers	Overall: RR = 0.77 (0.72-0.83) Men: RR = 0.66 (0.58-0.75) Women: RR = 0.85 (0.77-0.93) < 50years Old: RR = 0.76 (0.63-0.92) ≥ 50 Years Old: RR = 0.77 (0.71-0.86)
Sgadari et al.[30]	2000	3	Retrospective Cohort	9,752	7,733		Not Provided	Benzodiazepines	RR = 1.09 (0.98-1.19)
Tamiya et al.[31]	2015	3	Case Control	817		50+	Not Provided	Benzodiazepines	RR = 1.38 (1.09-1.72)
van Staa et al.[32]	2002	3	Case Control	231,778	121,615		Not Provided	Anxiolytics*	RR = 1.12 (1.12-1.15)
Vestergaard et al.[33]	2013	3	Retrospective Cohort	Not Provided	Not Provided	40+	Not Provided	Anxiolytics*	< 0.1 DDD/day: RR = 1.22 (1.17-1.27)* 0.1-0.33 DDD/day: RR = 1.38 (1.27-1.49)* ≥ 0.33 DDD/day: RR = 1.51 (1.39-1.63)*

*Includes benzodiazepines, diphenylmethane, carbamates, dibenzo-bicyclo-octadiene, azaspirodecanedione
**A specific benzodiazepine
Note: DDD = defined daily dose; RR = Risk Ratio; PAR = Population Attributable Risk; OR = Odds Ratio

Table 2. Risk of bias assessment of included studies using the ROBINS-I tool.

Authors	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviation from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Abrahamse et al.[21]	moderate	low	low	low	low	low	moderate	moderate
Axmon et al.[22]	moderate	moderate	low	low	low	low	low	moderate
Bakken et al.[23]	moderate	low	low	low	low	low	moderate	moderate
Bushnell et al.[24]	serious	moderate	low	low	moderate	moderate	low	serious
Coutinho et al.[25]	moderate	low	serious	low	low	low	low	serious
Herings et al.[26]	moderate	moderate	low	low	moderate	moderate	moderate	moderate
Hwang et al.[27]	moderate	moderate	low	moderate	low	moderate	low	moderate
Requena et al.[28]	moderate	low	moderate	low	moderate	moderate	moderate	moderate
Schlienger et al.[29]	low	low	low	low	low	low	low	low
Sgadari et al.[30]	moderate	moderate	low	low	low	moderate	low	moderate
Tamiya et al.[31]	serious	serious	moderate	low	low	moderate	moderate	serious
van Staa et al.[32]	moderate	moderate	moderate	low	low	moderate	moderate	moderate
Vestergaar et al.[33]	moderate	moderate	low	low	low	low	low	moderate

DISCUSSION

In this scoping review, anxiolytic medications were evaluated to determine if they put individuals at an increased risk of fracture. Overall, ATC Class N05B medications, as well as benzodiazepines, were studied more frequently in terms of fracture risk analysis. In patients utilizing either, there was an observed increased fracture risk according to numerous studies in this review, while another study reported decreased relative risk only in the lose dose cohorts. Therefore, it is important to consider the risk benefit analysis when prescribing these medications, especially in high risk populations, such as those over the age of 65 or those with independent risk factors such as chronic glucocorticoid use (defined as over three months of prednisone use (minimum 5 mg per day)), personal history of previous low energy fracture of the hip or spine, personal history of metabolic bone disease, chronic kidney disease more than or equal to stage 3 (GFR< 60 mL/min), high fracture risk as calculated by FRAX (fracture risk assessment tool), alcohol use (three or more units/d), vitamin D deficiency, current smoking, limited mobility, wheelchair bound, current cancer treatment (known to impact bone health), and diabetes mellitus (> 10 years and poor control).[34] Moreover, the inclusion of benzodiazepines as one of the medications in ATC Class N05B acts as selection bias for other medications in this group given the known risk for fracture specifically associated with benzodiazepines. As for zolpidem and beta blockers influence on fracture risk, each were only investigated in one study, respectively, which indicated more research needs to be conducted to identify the actual fracture risk associated with these medications.

Lastly, throughout the literature, a uniform method for statistically measuring and comparing fracture risk for medications was lacking. Within this review, 46% (6/13) of the articles did not quantify the amount of time a patient must be on a medication before considering that a fracture could be due to a medication. Additionally, more studies need to be conducted analyzing fracture risk in younger populations that do not have as many comorbidities. Plus, the medications investigated in multiple studies only listed "anxiolytics" and were not specified. Due to the ambiguity of the medications analyzed in the study, information gathered from these articles cannot be categorized. Lastly, the comorbidities of included patients were widely unavailable. There are numerous comorbidities that could be the cause of the resulting fractures which need to be revealed within the study population. These studies identified fracture risk in different ways, including relative risk, odds ratio, and percentage which made comparison difficult. Ultimately, for an increased understanding of the role anxiolytics play in fractures, additional research and a more consistent way of reporting information are needed. Future studies should include more specifics regarding medications being evaluated, including total daily dose and duration of use, the comorbidities of participants, and a uniformly accepted comparison strategy.

Limitations. A major limitation of this study included the paucity of literature regarding this subject, especially regarding zolpidem and beta blockers. With that said, a standardized comparison strategy must be established due to the inability to compare fracture risks. Moreover, the studies that met the inclusion criteria for this review did not include the concurrent medications and comorbidities of the patients in these studies. Lastly, sex, body mass index, and other patient demographics rarely were discussed, which contributed to confounding results in these studies and review.

CONCLUSIONS

Fractures are a mainstay of traumatic injuries and are accompanied by economical, physiological, and psychological hardship. With proper assessment and prophylactic measures, fracture risk can be reduced dramatically. Anxiolytic medications have been described widely to increase fracture risk, such as benzodiazepines in 60+ year old patients, and ATC Class N05B anxiolytics in 55+ year old patients.[22,25] Yet, some studies showed that at low doses, nitrazepam, as well as beta blockers, lowered fracture risk.[26,29] Ultimately, this scoping review helped to illuminate the inconsistency of anxiolytic fracture risk assessment while simultaneously illustrating the necessary steps to guide future research.

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