VOLUME 16 • MARCH 2023

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Effects of Smoking on Outcomes of Thyroid Eye Disease Treated with Teprotumumab: A Retrospective Cohort Study

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Received Dec. 20, 2022; Accepted for publication Feb. 14, 2023; Published online March 15, 2023
https://doi.org/10.17161/kjm.vol16.18940

ABSTRACT

Introduction. Smoking has been demonstrated to worsen the disease process and conventional treatment outcomes of thyroid eye disease. However, the effects of smoking on outcomes of thyroid eye disease treated with the novel therapeutic teprotumumab are currently unknown. Our study compares response to teprotumumab treatment between smokers and non-smokers with thyroid eye disease.

Methods. A single-center, retrospective cohort study was conducted. Inclusion criteria were patients diagnosed with thyroid eye disease who had started or completed therapy with teprotumumab at the time of our data collection. Main outcome measures included reduction in clinical activity score, diplopia, and proptosis.

Results. All smokers had type 2 thyroid eye disease prior to treatment and demonstrated less improvement in diplopia, proptosis, and overall clinical activity score compared to non-smokers with thyroid eye disease. There was no significant difference between smokers and non-smokers in baseline variables (sex, thyroid stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), number of infusions completed). Data analysis revealed a statistically significant difference in proptosis reduction between non-smokers and smokers.

Conclusions. Smoking is a modifiable risk factor which portends a worse response to treatment of thyroid eye disease with teprotumumab.

Kans J Med 2023;16:62-64

INTRODUCTION

Thyroid eye disease (TED) is a common manifestation of Graves' hyperthyroidism. Up to 50% of patients with hyperthyroidism will develop TED, of whom 3-5% will develop severe disease.[1-3] The precise pathophysiology is not understood fully, but TED is thought to occur due to activation of orbital fibroblasts by autoantibodies leading to subsequent orbital inflammation and connective tissue remodeling.[3] Clinical signs and symptoms of TED include lid retraction (present in up to 90%), exophthalmos, eye pain, diplopia, extraocular muscle myopathy, and vision loss in severe cases.[3,4] TED can be classified as type 1 disease which affects orbital fat without diplopia, or type 2 disease which is defined as diplopia within 20 degrees of fixation with restrictive myopathy.[5] TED severity can be graded using the Mourits Clinical Activity score (CAS) to guide management decisions.[6] Risk factors for TED include both genetic predisposition and environmental influences. Risk for developing TED is increased in women, patients with high serum cholesterol, those exposed to radioactive iodine therapy, and those who smoke.[1,7,8]

Smoking is a risk factor which consistently has been linked to development and worsening of TED.[2,3] It is the strongest modifiable risk factor, shown to both increase the severity of TED symptoms and decrease treatment response.[1,2] Patients with TED who smoke have been shown to have poorer response to treatments such as corticosteroids in comparison to non-smokers.[6]

Current management of TED has evolved over recent years to include use of immunomodulators with growing promise. Teprotumumab, a monoclonal antibody directed against insulin-like growth factor 1 receptor (IGF-1R), has demonstrated significant improvement in proptosis, CAS, diplopia, and quality of life compared to placebo for treatment of TED.[1,3,4,9] Teprotumumab can be used alone or in combination with corticosteroid therapy.[4,9] The effectiveness of teprotumumab treatment in smokers with TED has yet to be established. We hypothesized that the efficacy of teprotumumab will be reduced in TED patients who smoke compared to TED patients who do not smoke, similar to the reduced efficacy of other treatments seen in TED patients who smoke.

METHODS

A single-center, retrospective review of patients with TED treated with teprotumumab was conducted. Institutional Review Board approval was obtained and patients who had started or completed treatment with teprotumumab during the study were included. Data were analyzed using STATA (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC; USA). The differences between smokers and non-smokers in baseline characteristics as well as clinical response were assessed using Fisher's exact test for categorical variables and Wilcoxon rank-sum (Mann-Whitney) test for continuous variables. Statistically significant results were defined as $p < 0.05$.

RESULTS

A total of 34 patients with TED who were scheduled to begin teprotumumab were reviewed. Sixteen patients who began or completed treatment during the study were included in the initial comparisons. However, one patient did not have sufficient documentation, thus 15 were included in the statistical analysis (Tables 1 and 2). Six of the included 15 (40%) patients were current or former smokers. All the smokers in the study had type 2 disease, whereas all the non-smokers had type 1 disease (Figure 1).

The primary outcome assessed was change in CAS. Mean reduction in CAS was 3.7±2 in smokers, compared to 4.9±2.2 in non-smokers. Other variables assessed were change in visual acuity (VA), proptosis, and diplopia. VA outcomes were not significantly different between smokers versus non-smokers. All smokers had VA of 20/25 or better after receiving treatment with teprotumumab, except one patient who had a long-standing history of nystagmus and decreased visual potential whose vision remained stable and fluctuated between 20/30 and 20/40 OU.

Proptosis was reduced by 1.2±1.2 in the right eye and by 1.75±0.5 in the left eye in smokers versus by 4±1.4 in the right eye and 4.2±1.8 in the left eye in non-smokers. This reduction was found to be statistically

significant, as seen in Table 2.

Change in diplopia was not significant between the groups, but was more likely to be present initially in smokers compared to non-smokers (Figure 1). Of the 16 initially included, six of seven (85.7%) smokers had diplopia prior to treatment, whereas six of nine (66.6%) non-smokers had diplopia prior to treatment. One smoker and one non-smoker had resolution of diplopia with treatment. One smoker without diplopia prior to treatment developed complaints of diplopia after treatment.

Table 1. Baseline characteristics of 15 thyroid eye disease patients treated with teprotumumab, in terms of smoking status.

Variable	Categories	Total (%)	Non-Smokers	Smokers	p Value
Total		15 (100)	9 (60)	6 (40)	
Sex					0.10
	Females	13 (86.7)	8 (61.5)	5 (38.5)	
	Males	2 (13.3)	1 (50)	1 (50)	
Thyroid Stimulating Hormone TSH**		5.1 ± 12.7	6.2 ± 16.2	3.5 ± 5.2	0.80
Free Thyroxine T4**		1.9 ± 2.2	1.3 ± 0.7	2.7 ± 3.4	0.70
Free Triiodothyronine T3**		108 ± 136.8	131 ± 163.7	67.8 ± 73.6	1.00
Number of infusions**		5.7 ± 2.6	6.4 ± 2.4	4.5 ± 2.7	0.10

**Presented as mean ± Standard Deviation (SD).

Table 2. Differences in clinical response between the 15 patients based on smoking status.

Variable	Categories	Mean ± SD	Non-Smokers	Smokers	p Value
Total					
Reduction in CAS		4.4 ± 2.2	4.9 ± 2.2	3.7 ± 2	0.30
Diplopia**					
	Diplopia prior initiation of treatment	11 (73.3)	6 (54.6)	5 (45.4)	0.50
	Diplopia after initiation of treatment	5 (50)	3 (60)	2 (40)	0.50
Proptosis					
	Right proptosis prior	23.3 ± 2.4	24±2	22 ± 2.5	0.20
	Right proptosis after	19.9 ± 2.7	19.7 ± 3.2	20.3 ± 2	0.70
	Change in right eye proptosis	2.3 ± 2	4 ± 1.4	1.2 ± 1.2	0.02
	Left proptosis prior	24 ± 2.4	24.4 ± 2.2	23.4 ± 3	0.50
	Left proptosis after	20.4 ± 2.6	20.3 ± 3.3	20.5 ± 1.7	0.50
	Change in left eye proptosis	3.2 ± 1.9	4.2 ± 1.8	1.75 ± 0.5	0.04

**Presented as Total (%).

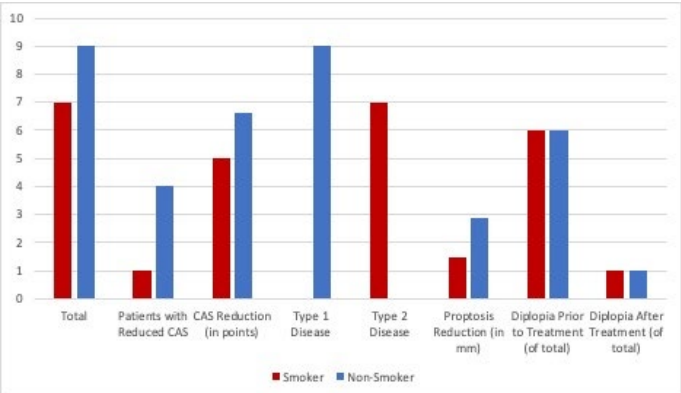

Figure 1. Patient characteristics in smokers and non-smokers.

DISCUSSION

Smoking is a modifiable risk factor known to be a causal factor increasing the risk and severity of thyroid eye disease. It is hypothesized that the causal association between smoking and TED may involve altered gene expression, cytokine production, and tissue hypoxia as well as other unknown components.[1,2] Aligned with our hypothesis, smokers demonstrated poorer response to teprotumumab treatment with regards to reduction of proptosis.

While our study agreed with the current literature regarding the effect of smoking on various treatments of TED, it was not without limitation. This was a single-center study with a small sample size which limited statistical power and generalizability to larger populations.

Additionally, only a small percentage of patients in our study completed the treatment course of eight infusions of teprotumumab. It will remain important to analyze the difference in treatment outcomes between smokers and non-smokers at the completion of treatment. Our patients were not stratified based on status as current smoker or ever smoker, and this too may alter the results, as smoking may have a dose-dependent effect on teprotumumab outcomes. More extensive research is needed to assess the long-term impact of smoking on teprotumumab efficacy. Despite these limitations, smoking cessation resources and counseling are crucial for those diagnosed with TED to prevent further disease progression and to prevent development of TED in those with thyroid dysfunction.[1,2]

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Keywords: thyroid eye disease, smoking, teprotumumab, proptosis, Graves orbitopathy

KANSAS JOURNAL of MEDICINE

Infection and Recurrence Rates in Rural Inguinal Hernia Repair

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Received Sept. 27, 2022; Accepted for publication Feb. 17, 2023; Published online March 15, 2023
https://doi.org/10.17161/kjm.vol16.18552

ABSTRACT

Introduction. Inguinal hernia repair (IHR) is a common procedure performed by general surgeons in rural community hospitals. Infection and recurrence rates for three types of IHR over two years at a rural Kansas hospital were analyzed. Previous research has shown outcomes regarding pain at six weeks were typically no different, and neither were long-term results, between open and laparoscopic techniques. However, there were fewer data showing the outcomes of these three hernia repair approaches in rural settings.

Methods. This was a retrospective, cross-sectional study using data collected from the electronic medical record (EMR) of a small hospital in central Kansas. Data from adult patients who had undergone IHRs over a two-year period (2018-2019) were deidentified and described using frequencies and percentages. This study used multi-variate logistic regression to examine the association of patient, surgeon, and surgical procedure characteristics on the occurrence of post-operative complications.

Results. Of the patients who received IHR, 46 were male and 5 were female. Mean age was 66 years, with a minimum of 34 and maximum ≥ 89 years. There were 14 total post-operative complications; two were superficial infections. There were no recurrences.

Conclusions. The sample size for each procedure type was too small to allow for statistical testing. However, the hospital had no recurrences. Future research should follow-up with this and other rural hospitals and perform a direct comparison of hernia surgery outcomes with those at a larger, more urban hospital, to understand potential differences by hospital size. ***Kans J Med 2023;16:65-68***

INTRODUCTION

An inguinal (groin) hernia is a common condition in which tissue or part of the intestine protrudes through a weakened area in the lower abdominal wall.[1-3] Inguinal hernias can be repaired three ways: open, laparoscopic, and robotic. In an elective repair, a mesh is placed from the inside of the abdomen to strengthen the wall. The most common post-surgical complications of IHR (of any type) include infection, seroma, hematoma, chronic groin pain, recurrence, sexual dysfunction with pain, and in males, ejaculatory disorders, and/or infertility.

The benefits of open repair techniques include decreased cost, shorter operation time, an option to be performed under local anesthesia, and ability to be performed by general surgeons.[1] Conversely, to gain access to the area, a larger incision must be used, thus nerve damage is a more common complication.[1,4]

When compared to the open repair, the laparoscopic repair has benefits of utilizing smaller (although multiple) incisions to gain access, ability to repair the contralateral side (if found to be bilateral), less post-operative pain and nerve damage,[5] and faster recovery time for the patient.[1,3,6,7] However, the operation costs more because it takes longer, utilizes general anesthesia, and utilizes specialized laparoscopic tools.

There also is a steeper learning curve associated with higher recurrence rates during the time of surgical training.[1,8,9] While post-operative complications were uncommon, they tended to be more severe when present.[3,6]

It is still debated whether one of these repairs is superior to the other; however, both have been found to be viable repair options.[3] Recurrence rates have been found to be no different between open and laparoscopic repairs, provided a mesh is used.[1,2] Outcomes regarding pain at six weeks were typically no different, and neither were long-term results.[9]

The study investigated the incidence of infection and recurrence associated with three methods of inguinal hernia repair (IHR) at the only hospital in a rural Kansas county, open plug-and-patch (OPP), open Lichtenstein (OL), and laparoscopic transabdominal pre-peritoneal (TAPP), to understand if there were differences in the rates of infection or rates of hernia recurrence by method.

METHODS

The rural hospital had not participated previously as a research site for surgical outcomes. The robotic method was not available. The EMR was updated in 2014, and exporting data was more challenging than anticipated.

This retrospective, cross-sectional study utilized EMR data on IHRs completed January 1, 2018 through December 31, 2019 at a rural hospital in Kansas. Inclusion criteria included IHRs performed on adult patients during the study period at the selected rural hospital. Exclusion criteria included patient was younger than 18 and emergency procedure (non-elective). Emergent procedures were excluded because a mesh is not placed due to the high risk for harboring infection.[10] Additionally, not placing a mesh had been shown to have higher hernia recurrence rates.

From the patient record, sex, age, insurance status, employment status, previous abdominal surgery, body mass index (BMI) category, smoking status, diabetes, immunocompromised status, and chronic conditions associated with cough or constipation were collected. For privacy purposes, any subject age over 89 was set at 89. The chronic conditions were chosen based on what the surgeons have believed to be linked with increased inguinal hernia risk. From the surgical record, location and type of inguinal hernia, operating surgeon, procedure used (OPP, OL, TAPP), and type of mesh were collected. From the follow-up history, data about post-operative complications were collected, including infection and recurrence.

Statistical Analysis. To achieve the objectives, descriptive statistics were calculated on the variables of interest. Bivariate tests were used to compare groups. Data were analyzed using multivariate logistic regression, with complication as a binary outcome variable (0 for no complication and 1 for a complication). All data were deidentified and analyzed using Stata SE 15. The University of Kansas Medical Center Institutional Review Board approved this study.

RESULTS

Of the 54 eligible charts reviewed, one patient was lost to follow-up. Two patients met exclusion criteria for incarcerated (emergent) surgery. Fifty-one patients' surgical procedures were included for analyses.

There were 46 males and 5 females. The mean age of IHR patients was 66 (SD 13.0), with a range of 34 to 89. Five (9.8%) patients were covered by Medicare, 25 (49.0%) by private insurance, and 19 (37.3%) patients had both Medicare and private insurance. There were two (3.9%) patients with an unknown insurance status. There were 24 (47.0%) patients who were employed full-time at the time of surgery, 21 (41.2%) who were retired, and 6 (11.8%) with an unknown employment status. Further detail is available in Table 1.

Table 1. Patient demographic characteristics.

Demographics	n (%)
Total	51 (100)
Gender	
Male	46 (90.2)
Female	5 (9.8)
Age	
≤ 59	14 (27.5)
≥ 60	37 (72.5)
Insurance Status	
Medicare	5 (9.8)
Private	25 (49.0)
Medicare + Private	19 (37.3)
Unknown	2 (3.9)
Employment	
Full-time	24 (47.0)
Part-time	0 (0)
Retired	21 (41.2)
Unknown	6 (11.8)

Two (3.9%) patients were characterized as underweight by BMI category, 23 (45.1%) as at a healthy weight, 17 (33.3%) as overweight, 6 (11.8%) as obese, and 2 (3.9%) as morbidly obese. One (2%) patient had an unknown BMI. There were 31 (60.8%) never-smokers, 7 (13.7%) with a past history of smoking, 7 (13.7%) current smokers, and 6 (11.8%) with an unknown smoking status. Two (3.9%) patients chewed tobacco. There were four (7.8%) patients with diabetes mellitus and eight (15.7%) who were immunocompromised. Eleven (21.6%) patients had disorders associated with increased abdominal pressure, such as cough or constipation. Nineteen (37.3%) patients had a previous history of abdominal surgery. Patients' risk factors are detailed in Table 2.

Table 2. Patient risk factors.

Body Mass Index Category	n (%)
Below 18.5	2 (3.9)
18.5-24.9	23 (45.1)
25.0-29.9	17 (33.3)
30.0-39.9	6 (11.8)
40.0+	2 (3.9)
Unknown	1 (2.0)
Smoking Status	
Never-smoker	31 (60.8)
Current	7 (13.7)
Past history of smoking	7 (13.7)
Unknown	6 (11.8)
Chewing Tobacco	
Current	2 (3.9)
Past history	0 (0)
Never	49 (96.1)
Diabetic status (Yes)	4 (7.8)
Immunocompromised (Yes)	8 (15.7)
Chronic cough or constipation (Yes)	11 (21.6)
Previous abdominal surgery (Yes)	19 (37.3)

There were 23 (45.1%) inguinal hernias on the right side and 24 (47.1%) on the left side. There were four (7.8%) patients who had bilateral hernia repairs. Fourteen (27.5%) hernias were direct and 37 (72.5%) were indirect. Five (9.8%) hernias were subtyped as sliding. Twelve (23.5%) patients had received previous IHRs, five (9.8%) of these being on the same side. There were 40 (78.4%) open (Lichtenstein), 9 (17.7%) open (Plug and patch), and 2 (3.9%) laparoscopic (TAPP). These data are detailed in Table 3.

Table 3. Hernia characteristics.

Side of Inguinal Hernia Repair (IHR)	n (%)
Right	23 (45.1)
Left	24 (47.1)
Bilateral (Yes)	4 (7.8)
Hernia Type	
Indirect	37 (72.5)
Direct	14 (27.5)
Hernia subtype - Sliding	5 (9.8)
Previous IHR (Yes)	12 (23.5)
Previous IHR on same side (Yes)	5 (9.8)
Surgical Procedure	
Open Lichtenstein	40 (78.4)
Open plug-and-patch	9 (17.7)
Laparoscopic transabdominal pre-peritoneal	2 (3.9)
Surgeon of Procedures	
Surgeon 1	39 (76.5)
Surgeon 2	10 (19.6)
Surgeon 3	2 (3.9)

Seven (13.7%) patients had post-operative complications, some with multiple complications. There was a total of 14 complications, all of which were minor. Two (28.6%) patients developed seromas, two (28.6%) developed hematomas, two (28.6%) had paresthesia at six weeks post-operative, three (42.9%) with groin pain at six weeks post-operative, two (28.6%) with superficial infections, one (14.3%) with urinary incontinence, one (14.3%) with testicular swelling, and one (14.3%) with blood during ejaculation. There were two patients who had a total of six complications. One patient had four complications, while the other had two. During the period of the study, there were no recurrences of inguinal hernia. Of these complications, 11 (78.6%) were performed by Surgeon 1, 2 (14.3%) by Surgeon 2, and 1 (7.1%) by Surgeon 3. However, the rates of complications by surgeon (# of complications over total patients for an individual surgeon) showed a different distribution: 11/39 (28.2%) for Surgeon 1, 2/10 (20.0%) for Surgeon 2, and 1/2 (50.0%) for Surgeon 3. These data are detailed in Table 4. The sample sizes for each procedure and complication type were too small to allow for statistical testing.

Table 4. Post-operative complications at follow-up.

Patients with Complications (n = 7)	n (%)*
Seroma	2 (28.6)
Hematoma	2 (28.6)
Paresthesia at six weeks	2 (28.6)
Groin pain at six weeks	3 (42.9)
Superficial infection	2 (28.6)
Urinary incontinence	1 (14.3)
Testicular swelling	1 (14.3)
Blood with ejaculation	1 (14.3)
Hernia recurrence	0 (0)

*Some patients had multiple complications.

DISCUSSION

This study aimed to determine differences in infection and recurrence rates in IHRs by repair type at a small rural hospital. While patient and procedure characteristics for a two-year period were described, the low volume of total IHRs limited the ability to apply statistical tests. However, clinical findings are discussed below, as well as the relevance of findings to rural hospital engagement in surgical quality improvement and to this hospital's and community's economic well-beings.

In terms of clinical findings, the study showed a higher incidence of IHR in males, consistent with other reports in the literature.[11,12] Due to the physiologic (embryologic) process, right indirect inguinal hernias occurred more often than left, because the right testicle takes longer to descend than the left and the processus vaginalis longer to obliterate.[11] No difference was found in incidence of right versus left hernia in this study, as they were nearly-equal in the sample.

Studies have demonstrated comparable outcomes between general hospitals and dedicated hernia repair centers.[13] Seven patients in our study experienced post-operative complications; however, these were all minor. An example of major complication would encompass returning to the operating room and/or admittance to the hospital for extensive care. The most common complication was groin pain at six weeks post-operative. There were only two superficial infections after open hernia repairs, and neither warranted removal and replacement of mesh.[14] No patients experienced inguinal hernia recurrences. This suggested that, in general, the quality of hernia operations at this hospital was good. One study cited a complication rate for open hernia repairs as 21.0%.[15] In another study, a review of 1,034 IHRs found that urgent or emergent repairs had a complication rate of 27%.[16] In comparison, elective repairs were found to have a complication rate of 15.1%.

Reducing quality measurement to percentages in rural surgery is problematic given its inherent low volumes.[17] The surgeon with the highest volume during our study period performed 39 hernia repairs and had a complication rate of 28.2%. One less complication would have lowered the rate to 25.6%, a difference of 2.6 percentage points. In a larger center, a surgeon performing 200 hernia repairs a year would experience only a 0.5 percentage point change for every one complication.

When potential risk-factors for post-operative complications were examined, the three of the seven patients who had complications were current smokers. In previous studies, smoking had been shown to be a modifiable risk factor for complications following hernia repair.[10,18] There were two patients who together cumulated 6 of the 14 total complications. Both of these patients had morbid obesity (a BMI of ≥ 40), which also has been shown to be a modifiable risk factor.[10,19,20]

Hernia repairs are considered "bread and butter" in rural surgery.[21] High-quality care remains the goal of all surgeons, but it should be acknowledged that quality's financial implications are growing as well. As quality measures become used more commonly in reimbursement policy, insurance contracting, and physician employment contracts, rural hospitals' ability to participate in quality improvement becomes increasingly crucial. Our rural hospital was a willing partner in this study, yet all were surprised by the difficulty of exporting and analyzing their data. Most rural hospitals do not have as many dedicated quality improvement personnel compared to their urban counterparts.[22] In addition, rural hospitals struggled to obtain and maintain robust information technology systems that facilitate routine, thorough quality improvement efforts.[17,23,24]

Given the importance of rural surgery to its hospitals and communities,[25] studies like these are important attempts to quantify rural surgical patient characteristics and surgeon performance. Nearly half of the procedures in our study were covered by private insurance. At the same time, 41.2% of patients were retired. This was explained, in part, by over one-third of patients utilizing both Medicare and private insurance coverage. This may mean that Medicare-eligible patients were working and covered by their employer-sponsored health benefits. Summing private coverage and dual Medicare/private coverage, 86.3% of these surgical patients were not Medicare-only patients. This proportion is in direct contrast to many rural hospitals, whose Medicare patients often exceed 60%.[17,25]

Limitations. This study was limited by its construction as a retrospective chart review that yielded a small sample size and narrow

distribution across surgical procedures and surgeons. Future studies should examine data from multiple rural hospitals to increase sample size and allow for a more robust analysis and leverage the growth of hospital systems, which more commonly include smaller, more rural hospitals, and utilize shared electronic medical records to compare outcomes from rural and urban hospitals.

CONCLUSIONS

Studying surgical outcomes at rural hospitals is vitally important. Surgeons need to be cognizant of their outcomes, not only for their own quality improvement efforts but chiefly due to consequences to patients, such as morbidity and mortality. Findings from this project should be used to inform rural general surgeons of the potential infection and recurrence rates associated with IHR by open (plug-and-patch or Lichtenstein) and laparoscopic (TAPP) techniques. This adds to the body of literature regarding IHR infection and recurrence rates. Rural surgeons also should be conscious of the impact of low volumes on their quality measures; small changes in raw numbers can mean larger changes in percentages. Future studies could be performed to compare data from rural and urban hospitals and facilitate greater rural surgeon engagement in quality improvement efforts.

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Keywords: inguinal hernia, general surgery, Kansas, infection, recurrence

KANSAS JOURNAL of MEDICINE

New-Onset Amyotrophic Lateral Sclerosis in a Patient who Received the J&J/Janssen COVID-19 Vaccine

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Received Jan. 5, 2023; Accepted for publication Feb. 7, 2023; Published online March 15, 2023
https://doi.org/10.17161/kjm.vol16.18969

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is a rapidly progressive neurodegenerative disease characterized by the degeneration of both upper and lower motor neurons.[1,2] This leads to progressive muscle weakness and eventual paralysis, with respiratory paralysis as the leading cause of death. It is considered to be an incurable disease with death occurring within two to five years of symptom onset.[3] Treatment usually targets symptom control with muscle relaxants for spasticity and speech therapy for dysarthria, involving a multidisciplinary team that can work on bulbar dysfunction, fatigue, and depression.[2]

Since first emerging as a pathogen at the end of 2019, Coronavirus 2019 (COVID-19) has caused significant global morbidity and mortality. As a result, safe and effective prophylactic vaccines were developed to contain this pandemic and curb its medical and economic consequences. Currently, there are three U.S. Food and Drug Administration-issued authorizations for the emergency use of the Pfizer-BioNTech, Moderna, and Janssen/Johnson & Johnson (J&J) COVID-19 vaccines. Data from large clinical trials indicated that the approved COVID-19 vaccines are safe and effective for most people.[4-6] However, the vaccines have been associated with multiple side effects, ranging from mild side effects such as headaches and fatigue to more severe side effects including anaphylaxis,[7] Guillain-Barré Syndrome, immune thrombotic thrombocytopenia, and myocarditis. We present one of the first cases of a previously healthy male who started experiencing symptoms of ALS after receiving the J&J viral vector COVID-19 vaccine.

CASE REPORT

A 47-year-old-male presented to the clinic with left-sided weakness, declining speech, dysphagia, and recurrent falls for nine months. His symptoms began one day after receiving the J&J/Janssen viral vector COVID-19 vaccine. Before the vaccine, he was a healthy right-handed mailman with no functional disability who walked about 10 miles every day. He had a past medical history of depression, anxiety, hypertension, and obesity, with a family history of diabetes, hypertension, and coronary artery disease in his mother, and amyotrophic lateral sclerosis (ALS) in his grandmother.

After receiving the J&J/Janssen COVID vaccine, the patient noticed symptoms on his left side. He first developed painful and tender inflammation at the injection site. Within one week, his symptoms developed into left-sided arm weakness and a weak hand grip. Over the next several months, this progressed to left upper and lower extremity weakness, declining speech dysphagia, and recurrent falls. Magnetic resonance imaging of his entire spine and brain was negative except for age-related degenerative defects and left-sided foraminal narrowing at C4-C5 and C5-C6.

On examination, he was found to have left arm fasciculations, left arm atrophy, spasticity, and hyperreflexia. Babinski's sign and Hoffman's sign were present bilaterally. He had spastic dysarthria, a sustained clonus at both ankles, and a pseudobulbar affect with intact sensory symptoms, coordination, and gait. Labs were unremarkable.

He was eventually referred to a neurologist and diagnosed with ALS with a pseudobulbar affect after electromyography. He was prescribed riluzole and followed up as an out-patient.

DISCUSSION

The presented case, although previously healthy, started experiencing symptoms of amyotrophic lateral sclerosis after administering the J&J viral vector COVID-19 vaccine. Although he was asymptomatic prior to the administration of the vaccine, he had a strong family history with his grandmother having a diagnosis of ALS.

Although the COVID vaccine remains the best preventive strategy for COVID-19, it has been associated with multiple side effects.[8-11] A recent study used the U.S Vaccine Adverse Event Reporting System (VAERS) and reported adverse events in 0.10% of patients receiving any COVID-19 vaccine. Of these, 33% were neurological symptoms representing 0.03% of all administered vaccines. Most of the neurological symptoms were mild. These included headaches, dizziness, and fatigue, most of which were reported after receiving the Janssen vaccine. However, some patients experienced serious adverse effects such as Guillain Barré Syndrome, transverse myelitis, cerebral venous thrombosis, and acute disseminated encephalomyelitis. They reported a weak association between ALS and the COVID vaccine with an incidence of 0.02, 0.01, and 0.00 cases per 1,000,000, respectively, for Pfizer, Moderna, and J&J Vaccines.[12]

A cumulative analysis review of post-vaccination adverse events was prepared by Pfizer after collecting cases reported to the health authorities. From December 1, 2020 through February 28, 2021, 501 cases of neurologic adverse events of special interest were studied (1.2% of the total adverse events). These cases included serious neurologic conditions such as, but not limited to, epilepsy, generalized tonic-clonic seizure, Guillain-Barré syndrome, multiple sclerosis relapse, and optic neuritis with no reports of ALS.[13]

We reported an unusual case of a newly diagnosed ALS following the J&J COVID-19 vaccination in a previously healthy individual. Although the precise pathophysiology remained unclear, it may be related to the enhanced immune response observed after administering the vaccine. This could trigger a neuroinflammatory response, ultimately leading to neurodegeneration and ALS. One study reported the rapid functional decline of two patients with slowly progressive ALS contracting COVID-19.[14] The authors theorized that the accelerated decline might be explained by the ability of COVID-19 to trigger neuroinflammation, hence supporting the hypothesis that the trigger could be either the virus itself or the immune response.

It is important to note that this patient's grandmother also had ALS, which may indicate a genetic predisposition. Further research is required to assess appropriate patient selection for administering the COVID-19 vaccine in patients with a past medical or family history of ALS.

With billions of vaccines delivered worldwide, rare adverse events and neuroinflammatory and neurodegenerative diseases increasingly are being reported. It is reasonable to consider that these adverse events temporally are associated with the vaccine instead of direct causation. Hence, the main limitation of our case report was the temporal relationship between COVID-19 vaccination and the onset of ALS.

CONCLUSIONS

This report highlighted several important teaching points. Firstly, it emphasized the need for ongoing surveillance and monitoring of adverse events following vaccination, especially in populations with unique medical histories or conditions. Secondly, it underscored the importance of conducting further research to understand the potential link between the vaccine and the development of ALS, particularly in light of the patient's family history. Finally, the case highlighted the importance of ongoing education and training for healthcare providers to stay informed about the latest research, guidelines, and best practices related to vaccine administration and safety.

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Keywords: amyotrophic lateral sclerosis, COVID-19, vaccine, safety

KANSAS JOURNAL of MEDICINE

Air Embolism as a Complication of Lung Biopsy and IV Contrast Administration

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Received Nov. 13, 2022; Accepted for publication Feb. 13, 2023; Published online March 15, 2023
https://doi.org/10.17161/kjm.vol16.18682

INTRODUCTION

Percutaneous computer tomography (CT)-guided needle biopsy (PCNB) of suspicious pulmonary nodules is a well-established method of obtaining tissue for histopathological examination.[1] Despite its wide use in the United States, this procedure carries with it a set of complications associated with significant morbidity and mortality.[2] Systemic air embolism (SAE) is a rare yet devastating complication of PCNB with longstanding cerebral and cardiovascular effects.

In this report, three cases are discussed. The first case involves an air embolus following CT-guided lung biopsy and leading to acute stroke. The second case was similar, with a CT-guided lung biopsy leading to acute-onset neurologic symptoms. The third case, while it did not involve a percutaneous lung biopsy, highlighted the risk of air embolism with procedures as routine as IV contrast administration for the purposes of obtaining a CT scan.

CASE REPORT

The first case was a 71-year-old male patient with a medical history significant for hypertension, as well as heavy tobacco and alcohol use, presenting for CT-guided biopsy of a right lower lobe pleural-based mass. During the biopsy, the patient developed a mild cough and hemoptysis, but the procedure was overall well-tolerated. Post-procedural imaging showed no pneumothorax, but demonstrated pulmonary hemorrhage at the site of the biopsy.

A post-biopsy CT scan showed a small amount of air within the non-dependent portion of the mid descending thoracic aorta (Figure 1). The patient was immediately placed in the head down/right-side down position, started on 100% high-flow oxygen, and closely monitored. The CT scan was repeated after one hour showing resolution of the air embolus. Orders were placed for an overnight admission for observation; however, the patient declined and was discharged against medical advice. He was advised to come back if he developed chest pain or shortness of breath.

The following day, the patient presented to the emergency department (ED) for difficulty urinating, lower abdominal pain, and difficulty to ambulate due to lower extremity weakness. On physical exam, the patient had 5/5 motor strength in both upper and lower extremities, as well as intact sensation and 2+ reflexes, however, he exhibited unsteady gait. CT scan of the head showed no evidence of ischemia or hemorrhage. Brain magnetic resonance imaging (MRI) showed multiple focal areas of acute ischemia, predominantly in the posterior left cerebellum and left parietal lobe, as well as punctate foci in the left medullary pyramid, left midbrain, and right parietal lobe (Figure 2). The patient was considered to have an acute cerebrovascular accident secondary to air emboli and was transferred to a nearby stroke center for further management.

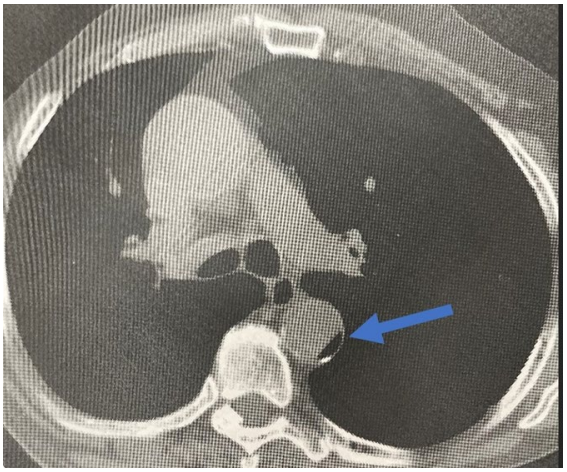

Figure 1. Chest CT scan showed an air embolus within the aorta (blue arrow).

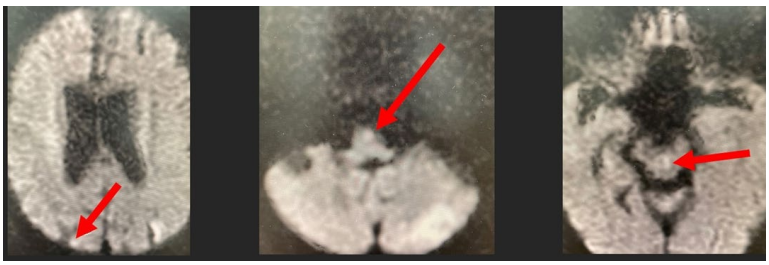

Figure 2. Brain MRI showed multiple areas of acute ischemia (red arrows).

The second case was a 75-year-old male with a past medical history of hypertension and benign prostate hyperplasia who presented to the radiology department for a CT-guided lung biopsy. A previous positron emission tomography had demonstrated a hypermetabolic lesion in the left upper lobe of his lungs. The patient underwent successful CT-guided biopsy of the lesion. Immediately after the procedure, he was unable to move his right arm or squeeze the hand of the bedside registered nurse. Soon after, he developed right lower extremity weakness and expressive aphasia.

A stroke alert was activated, and the patient was transferred to the ED. Upon arrival, the patient's neurological symptoms had resolved. The initial National Institutes of Health Stroke Scale (NIHSS) score was documented to be 0 in the ED. The ED physician consulted a tele-neurologist who recommended against administration of tissue plasminogen activator and recommended medical evaluation for transient ischemic attack (TIA).

CT of the patient's brain revealed no acute intracranial abnormality. The patient was given a 325-milligram (mg) dose of aspirin and was admitted for medical evaluation. He was started on a high intensity statin and clopidogrel in addition to his aspirin. He underwent neurological checks every four hours without any documented neurological deficits.

Review of the patient's medical record revealed a normal carotid ultrasound, which was completed almost a year prior to presentation. This study was ordered for further evaluation of dizziness by his

primary care physician. Post biopsy CT images were reviewed after the stroke alert, and they demonstrated mild expected local hemorrhage, as well as a small anterior pneumothorax. No air embolism was visualized in the pulmonary vessels or the heart. The patient underwent MRI and magnetic resonance angiography (MRA) of his brain and bilateral carotid vessels, respectively.

The MRI of the brain was negative for acute territorial ischemia, hemorrhage, or mass, but it demonstrated a few scattered foci in the periventricular and deep white matter, likely due to chronic microvascular ischemic changes. The carotid MRA demonstrated patent vessels without intraluminal narrowing. An echocardiogram with a bubble study showed normal ejection fraction, normal valvular morphology, and no evidence of a patent foremen ovale.

For the evaluation of risk factors, a complete blood count, complete metabolic panel, fasting lipid panel, and glycated hemoglobin (A1c) tests were obtained. A1c was 6.1%; all other tests were in the normal range. Given the onset and resolution of neurological symptoms and an otherwise negative work up for TIA, the patient was diagnosed with transient neurological deficits secondary to an air embolism. Upon discharge, his clopidogrel was discontinued and his statin dose was lowered to medium intensity due to his age and elevated atherosclerotic cardiovascular disease risk.

The third case involved a 73-year-old male patient with a medical history of alcohol dependence, tonsillar cancer status post radiation in 2010, generalized anxiety disorder, and benign prostate hyperplasia who presented to his primary care physician for annual follow-up. During the visit, the patient reported several weeks of bloating, postprandial vomiting, weight loss, in addition to not having any bowel movements or flatus for a few days. Given these symptoms, the patient was sent to the ED for workup of bowel obstruction. Upon arrival, a CT scan of the abdomen with IV contrast showed partial small bowel obstruction which was managed conservatively with NPO status, nasogastric tube placement, and therapeutic Gastrografin enema.

In addition to these findings, the CT scan showed air in the right ventricle. The cardiothoracic team recommended no surgical intervention at the time. The hospital's cardiology team recommended the Trendelenburg position, which requires placing the patient supine with the head at a 15-30 degree angle below the feet, with close monitoring of the patient's clinical status. The next day and on follow-up imaging, the air embolism in the right ventricle was found to have resolved. In addition, the patient's small bowel obstruction improved, and he had several bowel movements during his hospital stay.

Given the lack of procedures performed on the patient's initial presentation to the ED, and in the absence of otherwise identifiable risk factors, the cause of the air embolism was attributed to the IV access obtained for the purpose of IV contrast administration. Figure 3 is a CT image showing an air embolus in the right ventricle.

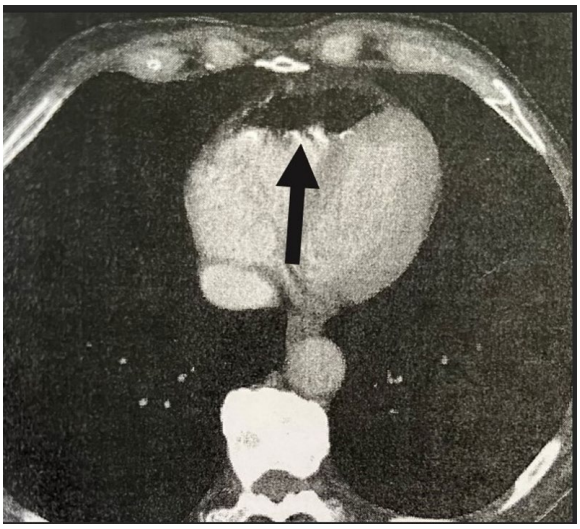

Figure 3. Air embolism was seen in the right ventricle (black arrow).

DISCUSSION

SAE is classified as venous or arterial depending on the mechanism of gas entry into the bloodstream. Systemic arterial air embolism, rather than systemic venous embolism, is the major concern in percutaneous lung biopsy and occurs when air enters the pulmonary venous system and reaches the systemic circulation.[3] Identified risk factors for development of SAE include depth of the needle in the lesion, number of samples, endotracheal anesthesia, location of the lesion above the level of the left atrium, and prone and right lateral decubitus position of patient.[4,5] Furthermore, case studies have noted patient coughing as a presumed factor that increases the risk of air embolism due to the increased pressure gradient between the airway and pulmonary vein.[6] However, this is an unpreventable risk factor and there were no available data to differentiate the effects of a chronic cough or an acute episode of coughing during the procedure on the risk of an air embolus occurring.

Incidence of clinically apparent SAE was estimated at 0.061%, while clinically silent SAE may be as high as 3.8%.[7] This reported rate was less than the actual rate of SAE most likely because cases are often asymptomatic and not diagnosed.[3] When evident, clinical manifestations of SAE are varied with the most serious concerns being involvement of the cerebral and cardiovascular systems. Typically, patients present with symptoms of end-artery obstruction, such as cardiac arrhythmias, hypotension, drowsiness, dysphasia, stroke-like facial and limb weakness, seizures, and acute dyspnea.

Characterizations of the risk of venous air embolism in patients receiving intravenous contrast have been made. A study of 677 patients who underwent CT with IV contrast observed an incidence of 11.7%.[8] The air emboli varied in size, ranging from less than 1 cm to up to 2 cm in diameter, and found predominantly in the pulmonary artery. Given the small yet quantifiable risk of air embolism with procedures that necessitate intravenous access, knowledge of this phenomenon may reduce time to diagnosis and intervention in the symptomatic patient.

Early recognition of SAE is critical because simple temporizing measures have shown to lead to better outcomes.[2,3] Monitoring patient vitals and starting 100% high-flow oxygen therapy to treat hypoxia, as well as eliminate the gas from the bubbles is critical. Administration of supplemental high flow oxygen aids in the reabsorption of nitrogen

back into the blood, which in turn eliminates gas bubbles, as well as aids in overall oxygenation.

The role of hyperbaric oxygen therapy as first-line therapy is well defined.[2,3] The rationale behind this therapy is to reduce the mechanical obstruction of the embolus, to promote the conversion of nitrogen in the embolus to its soluble form, and to increase oxygen delivery to metabolically active tissues. Additionally, in the setting of arterial embolism, placing the patient in the right lateral decubitus position traps the air in the left ventricle and prevents it from entering the systemic circulation. After providing initial resuscitative and supportive measures, CT of the head and chest can be used to confirm the diagnosis of SAE, as well as rule out other complication of PCNB such as pneumothorax.[3] Approaching complications status-post PCNB with a wide lens can help to capture the diagnosis of SAE and trigger the initiation of a treatment algorithm to promote better outcomes.

CONCLUSIONS

While procedures like CT-guided lung biopsy and IV contrast administration are indispensable tools for modern medicine, they are not risk-free. In fact, the introduction of any foreign object into the human body for the purposes of diagnosis or treatment carries a risk/benefit profile that needs to be assessed and made clear to the patient in the process of obtaining their informed consent. Although the complication of post-procedural air embolism is not common, its occurrence should be considered a possibility given the wide range of clinical outcomes that can result from it. From being completely asymptomatic, to causing self-resolving symptoms, to being a cause of mortality, air embolism can be unpredictable depending on its location. For this reason, it is vital to keep this differential diagnosis in mind when treating a patient who recently had a procedure done, even if it is as simple and routine as an IV-line placement (the rate of air embolism post IV contrast administration, although asymptomatic in most cases, has been reported to be as high as 23%[9]). In doing so, physicians can identify this entity at an earlier stage and plan accordingly based on the patient's symptoms and clinical status, as well as on the location of the air embolism.

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Keywords: air embolism, image-guided biopsy, contrast media

KANSAS JOURNAL of MEDICINE

A Case Series of Spouses Undergoing Rapid Micro-Induction Technique of Buprenorphine Initiation from Methadone

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Received Aug. 19, 2022; Accepted for publication Feb. 13, 2023; Published online March 15, 2023
https://doi.org/10.17161/kjm.vol16.18433

INTRODUCTION

The impact of opioid use disorder (OUD) and opioid fatal overdoses continues to be a substantial source of lost economic value in the United States.[1] In 2017, the overall economic burden attributed to OUD and fatal overdoses totaled approximately $1.02 trillion, with $35 billion attributed to healthcare costs and $3.5 billion to OUD treatment. Medications used to treat individuals with OUD have demonstrated a reduction in the prevalence of opioid misuse, as well as the number of opioid overdose fatalities.[2,3] Historically, the population requiring treatment has outnumbered the capacity of available treatment.[4] The situation necessitates the implementation of safe and efficient treatment strategies for patients, while seeking cost-conscious solutions to address the rising economic burden on the healthcare system. Presently, individuals undergoing daily methadone treatment can anticipate an average annual cost of $6,552. Those who undergo buprenorphine treatment twice weekly may expect $5,980 annually, highlighting a savings of over $500 comparatively.[5]

There are three medications approved by U.S. Food and Drug Administration for Medications for Opioid Use Disorder (MOUD) treatment that target the opioid receptors: methadone, buprenorphine, and naltrexone.[6] Methadone is a full opioid agonist at the opioid receptor and is by far the oldest, evidence-based effective treatment for OUD. However, methadone has some limitations as it cannot be prescribed and is dispensed only by Opioid Treatment Programs, which are regulated federally and by the State. During the course of methadone treatment, patients face various constraints including daily clinic visits, the requirement to drink the formulation in the presence of staff, and participation in mandated counseling. Patients are allowed to take home the medication only after being enrolled in the program for a while, which may cause conflicts with their personal schedules.

Buprenorphine is used for the maintenance treatment of OUD.[6] Buprenorphine has potential advantages over methadone, including a lower overdose risk, a "ceiling effect" for respiratory depression, fewer pharmaceutical interactions, and the absence of risks of QTc-prolongation. It also can be prescribed for the employed and childbearing age groups.

Buprenorphine has a partial intrinsic activity but has a high affinity at the mu-opioid receptors.[6,7] Hence, if administered concomitantly with a full agonist, it potentially can displace the full agonist and cause a sudden, precipitated withdrawal. Traditional buprenorphine induction protocol requires full abstinence from opioid agonists for a period of 24 to 72 hours before initiation.[6,8-10] This can be challenging for patients who are taking methadone and trying to taper the dose, due to the need to stop or switch therapies. This can predispose them to withdrawal symptoms and cravings, threatening potential relapse.[6,11]

Micro-dosing or micro-induction is the practice of administering small escalating doses of buprenorphine to obtain benefit from its action with minimal side effects. This technique implies a slow build-up of buprenorphine at the opioid receptors with repeated small doses bypassing the precipitated withdrawal.[8,12-14] The literature review on micro-dosing techniques showed that most of them primarily have been performed in an inpatient setting.[15-18] Only a few transitions were performed in an outpatient setting.[19] Our case series was innovative as a successful transition from methadone to buprenorphine was described in two patients, using the micro-dosing technique in an outpatient setting.

CASE REPORT

A married couple, a 44-year-old male and a 43-year-old female, were evaluated at our facility for OUD. They were previously on methadone for the treatment of OUD and were transitioned successfully to buprenorphine via rapid micro-induction. The rapid micro-induction procedure was performed in an outpatient setting with ancillary medications administered for withdrawal symptom relief. Both patients were assessed and followed on-site by a team composed of an addiction psychiatrist, nursing staff, and an addiction fellow.

Patient A was a 44-year-old male patient with a past psychiatric history (PPH) of OUD and attention-deficit/hyperactivity disorder (ADHD) on treatment with methadone 50 milligrams (mg) for the past nine years. He had been stable on that regiment without any complications, but sought a change in treatment due to transportation difficulties and the driving distance to the clinic. Additional past medical history included melanoma and renal cell carcinoma status post left nephrectomy. He was started on hydromorphone and various prescription opioids following his left nephrectomy. The patient had chronic bilateral knee pain in addition to his post-surgical pain which was managed with opioid therapy. He then developed tolerance to the opioids, started to increase the dosage and frequency of opiates, and obtained them illicitly from the streets. He was diagnosed with OUD, started on methadone, and nine years later he decided to switch therapies.

Patient B was a 43-year-old female patient with a past medical history of hypothyroidism, PPH of OUD, and ADHD and was on treatment with methadone 67 mg. There were no reported issues or side effects with methadone, but she wanted to make the change to buprenorphine for reasons similar to her husband, including her job, transportation, and children at home.

Rapid micro-dosing of buprenorphine technique was explained to the patients, and they expressed interest in this method. For patient A, the micro-induction procedure began with a 2 mg sublingual film of buprenorphine. The film was divided into four parts of 0.5 mg buprenorphine that was administered in intervals of one-half to one

hour under direct supervision in the clinic. Following complete dosing, 50 mg of methadone was administered.

The Clinical Opiate Withdrawal Score (COWS) scale was used to quantify the severity of opiate withdrawal.[19] The COWS scale establishes severity ranges based on patients' signs or symptoms in the following manner: Scores 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal.[20] COWS was obtained at the start of micro-dosing and thirty minutes after completion (Table 1). Mild withdrawal symptoms of sweating, chills, fatigue, and nausea were observed on the first day with a COWS score of 9.

The dose of buprenorphine was increased to 3 mg on day two, followed by the administration of 50 mg of methadone. On day three, patient A was scheduled to take 6 mg of buprenorphine, but decided to take 4 mg to align his treatment course with his wife. On this day, he reported feeling anxious and had a COWS of 0. On day 4, he was administered 8 mg buprenorphine with methadone dosing. On day 5, he started on 12 mg of buprenorphine at home and discontinued methadone. He returned to the clinic the following week dosed at 16 mg buprenorphine, but reported cravings and mild withdrawal symptoms. He expressed interest in increasing the dosage greater than 16 mg. At that time, he was switched to 20 mg daily and entered the stabilization phase of buprenorphine treatment.

Patient B followed a similar treatment course, but needed an additional day of micro-induction to achieve the complete transition from methadone to buprenorphine. Micro-dosing of buprenorphine was followed by administration of 67 mg of methadone. She stopped her levothyroxine for hypothyroidism several days prior to starting micro-induction due to concern about medication interaction. On day one, she was started on 1 mg buprenorphine, but began to display withdrawal symptoms (chills, fatigue, nausea, myalgias, and anxiety) and had a COWS of 12. At that point, micro-induction was stopped, and methadone was dosed at 67 mg. The patient was administered hydroxyzine 25 mg and clonidine on day one and continued to receive them on days two and three (Table 2).

On day two, she was administered 2 mg buprenorphine and had a COWS of 8, reporting chills, fatigue, abdominal pain, diarrhea, nausea, itching, tremors, and headaches. On the third and fourth days, the patient was dosed with 4 mg and 8 mg of buprenorphine, respectively. On both days, the patient denied having withdrawal symptoms. The following days occurred over the weekend and her dose was increased to 16 mg. She reported having headaches, low energy, and insomnia over both days. She stated that she felt more comfortable at 12 mg and did not want to increase the dose.

Both the patients transitioned successfully to buprenorphine. Four days were required for patient A and five days for patient B to complete the transition, including a day for initial assessment and half days dedicated to clinical care. On follow-up in four weeks, both the patients were stable on buprenorphine and did not report relapse.

DISCUSSION

Two patients were transitioned from agonist therapy of methadone to sublingual buprenorphine in an outpatient setting in a short period of four to five days. The patients reached a therapeutic dose of buprenorphine while taking 50 mg (patient A) and 67 mg (patient B) daily without requiring a period of opioid withdrawal prior to initiation and tapering the daily dose of methadone. Supportive medications, such as hydroxyzine and clonidine, were used effectively as needed to counter any withdrawal symptoms. Following micro-induction for patient B, she was maintained on buprenorphine and did not experience withdrawal symptoms or cravings for illicit opioids. Patient A reported some withdrawal symptoms after completing micro-induction, which was addressed by increasing his dosage of buprenorphine slightly.

These cases illustrated that barriers to buprenorphine treatment can be overcome by unique techniques like above.[9] Utilization of rapid micro-induction confers many benefits for both patients and physicians by reducing the amount of time patients need to visit the clinic, removing the need to be in withdrawal prior to induction, and having added flexibility of dosing. The cases demonstrated that modifications to micro-doses transitioning from a full agonist to a partial agonist can be tailored to assist patients on an individual basis. Personalized transition creates a better experience for patients by reducing the overall burden of withdrawal and further compliance with MOUD.[9]

Table 1. Detailed information for Patient A.

			Dose 1	Dose 2	Dose 3	Dose 4	Total
Day 1	BPN (mg)		0.5	0.5	0.5	0.5[1]	2.0
	COWS	Before	9	9	7	7	
		After	9	8	7		
	Vitals		HR 87 RR 18 BP 133/79 SpO2 99% Temp 97.8	HR 77 RR 17 BP 135/76 SpO2 98%	HR 77 RR 16 BP 118/79 SpO2 97%	HR 79 RR 17 BP 143/85 98% SpO2	
	Withdrawal Symptoms		Pulse Chills Restlessness Mild diffuse discomfort Tearing eyes Nausea Anxiety Irritability	Chills Restlessness Mild diffuse discomfort Moist eyes Nausea Yawning Anxiety	Sweating/ chills Inability to sit still Moist eyes Diffuse discomfort Irritability/ anxiousness	Sweating Inability to sit still Diffuse discomfort Nausea Anxiety/ irritability	

			Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Total
Day 2	BPN (mg)		0.5	0.5	0.5	0.5	0.5	0.5[1]	3.0
	COWS	Before	4	4	7	0	1	6	
		After	4	7	0	1	6	16	
	Vitals		HR 84 RR 18 BP 135/78 SpO2 99% Temp 98.4	HR 84 RR 17 BP 127/81 SpO2 99%	HR 80 RR 17 BP 126/69 SpO2 98%	HR 78 RR 17 BP 133/83 SpO2 99%	HR 75 RR 17 BP 123/75 SpO2 100%	HR 74 RR 16 BP 131/82 SpO2 99%	
	Withdrawal symptoms		Pulse Sweating/ chills Stomach cramps Irritability/ anxiousness	Pulse Sweating/ chills Stomach cramps Irritability/ anxiousness	Beads of sweat on face Nausea Slight tremor observable	None	Yawning	Sweating Frequent shifting Nose running Stomach Cramps Slight tremor Irritable/ anxious Piloerection	

			Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Total
Day 3	BPN (mg)		0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5[1]	4.0
	COWS	Before	5	4	1	0	0	0	0	0	
		After	-	4	-	0	0	0	0	0	
	Vitals		HR 88 RR 17 BP 126/82 SpO2 99% Temp 97.8	HR 82 RR 16 BP 138/78 SpO2 97%	HR 81 RR 17 BP 132/75 SpO2 97%	HR 79 RR 16 BP 130/76 SpO2 100%	HR 73 RR 18 BP 144/81 SpO2 99%	HR 74 RR 17 BP 132/71 SpO2 97%	HR 76 RR 18 BP 130/76 SpO2 96%	HR 75 RR 19 BP 143/88 SpO2 98%	
	Withdrawal symptoms		Pulse Chills Nausea	Pulse Chills Nausea	Pulse	None	None	None	None	None	

[1]Upon completion of last BPN dose, 50 mg of methadone was administered daily.

Table 2. Detailed information for Patient B.

			Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Total
Day 1	BPN (mg)		0.5	0.5[1]							1.0
	COWS	Before	0	-							
		After	-	12							
	Vitals		-	-							
	Withdrawal symptoms		Chills Fatigue Nausea Myalgias Irritability/ anxiousness	Chills Fatigue Nausea Myalgias Irritability/ anxiousness							
Day 2	BPN (mg)		0.5	0.5	0.5	0.5[1]					2.0
	COWS	Before	8	4	2	1					
		After	4	2	1	1					
	Vitals		HR 104 RR 18 BP 133/82 SpO2 92% Temp 97.8	HR 94 RR 17 BP 130/84 SpO2 100%	HR 86 RR 16 BP 125/85 SpO2 100%	HR 87 RR 17 BP 116/75 SpO2 100%					
	Withdrawal symptoms		Pulse Loose Stools Flushing/ sweating Difficulty sitting still	Pulse Loose stools Irritability/ anxious	Pulse Chills/ flushing	Pulse					
Day 3	BPN (mg)		0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5[2]	4.0
	COWS	Before	3	1	2	0	1	0	0	1	
		After	1	2	0	1	0	0	1	1	
	Vitals		HR 95 RR 17 BP 135/83 SpO2 100 % Temp 97.8	HR 88 RR 16 BP 116/81 SpO2 100%	HR 103 RR 17 BP 130/76 SpO2 100%	HR 78 RR 16 BP 108/65 SpO2 97%	HR 89 RR 17 BP 121/81 SpO2 98%	HR 75 RR 16 BP 119/74 SpO2 99%	HR 72 RR 16 BP 116/74 SpO2 99%	HR 98 RR 16 BP 126/93 SpO2 100%	
	Withdrawal symptoms		Pulse Nausea Loose stool	Pulse	Pulse	None	Pulse	None	None	Pulse	

[1]Addition of clonidine and hydroxyzine 25 mg given after second dose due to withdrawal symptoms on Day 1 and then prior to first dose for Day 2 and Day 3.
[2]Upon completion of last BPN dose, 67 mg of methadone was administered daily.

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Keywords: opioid use disorder, methadone, buprenorphine, case studies

KANSAS JOURNAL of MEDICINE

Severe Laryngeal Edema after Extubation with Prior Use of ACEi Medications

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Received Dec. 21, 2022; Accepted for publication Feb. 13, 2023; Published online March 15, 2023
https://doi.org/10.17161/kjm.vol16.18945

INTRODUCTION

Angioedema (AE) is a known adverse effect of angiotensin-converting enzyme inhibitor (ACEi) therapy, usually seen in the outpatient setting shortly after initiating treatment, but also can occur after months or years.[1] The prevalence of ACEi-induced AE has been reported as 28% to 30%.[2] AE is believed to be caused by plasma extravasation secondary to increased vascular permeability within the dermis, subcutaneous, or submucosal tissue.[3] Activation of the kallikrein-kinin system and the classic complement pathway results in the release of inflammatory mediators that lead to vasodilation.

Among patients presenting with AE, facial edema was seen in 85%, followed by lingual swelling in 40% and laryngeal edema in 10%; the condition is self-limiting, with spontaneous resolution of swelling often within two to three days.[4-6] Immediate management of AE focuses on airway protection, as respiratory failure may ensue secondary to airway edema and complete obstruction. In patients with hoarseness, odynophagia, or dyspnea, fiberoptic nasopharyngolaryngoscopy can be a useful technique to evaluate for laryngeal edema.[5,7]

This case reports a patient with a previous history of ACEi use who presented with severe laryngeal edema 20 minutes following extubation. Multiple attempts at reintubation were made utilizing an awake Glidescope™ technique, fiber optic, and blind nasal tube placement.

CASE REPORT

Written, informed consent was obtained from the patient for publication of this case report.

A 67-year-old, 105 kg Caucasian male with atrial fibrillation, insulin-dependent diabetes mellitus, obstructive sleep apnea, and hypertension presented to the operating room for incision and drainage of a left foot wound infection. Notably, the patient reported two previous instances of throat swelling while taking ACEi medications, one of which required intubation. Therefore, he had listed allergies to this class of medication and had discontinued them for two years prior to this incident. On inspection of the oral cavity, the patient had a Mallampati III opening, adequate thyromental distance, and normal dentition. Other than the left foot infection, his vital signs and physical examination were unremarkable.

After the application of routine monitoring devices and premedication with midazolam 1 mg IV, anesthesia was induced with 150 mcg of fentanyl, 100 mg succinylcholine, 200 mg propofol, and 50 mg ketamine IV. Direct laryngoscopy with a Miller 2 blade revealed a Cormack-Lehanegrade-one view, and the patient was intubated without difficulty. Anesthesia was maintained with sevoflurane and the operation was uneventful. Following this case, the patient was extubated without incident, and he was transferred to the post-anesthesia care unit (PACU) with supplemental oxygen for monitoring. The patient's intraoperative course lasted 30 minutes with 20 minutes of tourniquet time.

Hemodynamics were stable upon arrival to PACU. Approximately 20 minutes later, the nurse noted the patient's oxygen saturation had dropped to the mid-90s with swelling at the base of his tongue and no systemic signs of anaphylaxis or subcutaneous emphysema. The patient received 8 mg dexamethasone, 50 mg diphenhydramine, and 20 mg famotidine. Respiratory therapy was called for inhaled racemic epinephrine and a nasopharyngeal airway was inserted.

Despite these efforts, the patient's tongue continued to swell, and intubation was deemed necessary, so the surgery team was notified of possible surgical airway intervention. Initially, an awake Glidescope™ was attempted but was unsuccessful secondary to severe supraglottic and glottic swelling with copious secretions. A fiberoptic scope was introduced for a nasal approach. This was complicated by desaturations to the mid-forties, so bag-mask ventilation was performed while continuing the intubation attempt. Saturations improved to within normal range, but ultimately the tube could not advance through the vocal cords.

A smaller diameter tube was introduced blindly through the nasal passage. Color change capnometry was negative for end-tidal CO_2 and no breath sounds were noted. Bag ventilation was performed through this tube while a Glidescope™ was introduced to visualize the tube's position. Visualization of laryngeal structures was achieved, and the nasal tube was advanced successfully through the cords. Afterward, the patient was transferred to the intensive care unit where he remained intubated for the next two days, during which time he received systemic steroids. He was extubated without incident and discharged home on post-operative day three.

DISCUSSION

The differential diagnosis of post-operative laryngeal swelling includes AE, allergic reaction, anaphylaxis, peritonsillar abscess, hematoma, and superior vena cava syndrome.[8] The patient lacked systemic symptoms, hypotension, and anaphylactic or allergic manifestations, and the physical exam did not indicate hematoma formation. However, he expressed bilateral, soft, non-pitting edema evident of AE. Moreover, he had multiple predisposing conditions that can lead to the diagnosis of AE, including prior use of ACEi medications and a previous episode of AE that required intubation. The patient's symptoms presented in the immediate post-operative period, and recent airway manipulation has been reported to precipitate AE.[5,9]

Inciting factors often are idiopathic, yet 38%-68% of acquired forms arise following the use of ACEis, which interfere with the conversion of angiotensin I to angiotensin II and cause a reduction in the degradation of bradykinin.[3,6,8] Other medications include certain antibiotics, opioids,[7] NSAIDs,[10, 11] and angiotensin II receptor antagonists.[12] The latter is a unique association in that antagonizing the angiotensin II receptor does not increase kinin levels, suggesting a different mechanism may be involved. Additional forms of AE follow a hereditary

pattern and involve deficiencies in the C1 esterase inhibitor protein.[13] These patients are susceptible to acute swelling after physical, dental, or surgical manipulation of the upper airway.[14] Our patient did not have any measurements of C4, C1q, or any functional assays of the complement cascade available for reference.

Varying degrees of laryngeal edema are seen in patients post-extubation. Among patients requiring reintubation, 15% are due to post-extubation laryngeal edema.[9] Other than extubation predisposing to laryngeal edema-indicated reintubation, pre-hospital use of ACEi was found to be an independent risk factor for failed extubation due to unexpected upper airway edema.[15] These two different etiologies often overlap in hospital settings, making it difficult to identify the precise cause of an individual case, though management was often the same.

When AE is suspected, primary management requires discontinuation of the offending agents and evaluation of the airway. Though AE is self-limiting, it is crucial to identify the natural regression of AE to prevent unnecessary surgical intervention. Chiu et al.[16] produced an algorithm for airway management in the AE setting. They categorized AE into three types based on the extent of swelling: Type 1 involves swelling of the face and oral cavity only, Type 2 extends to the floor of the mouth or tongue, and Type 3 extends to the supraglottic structures. In the study, 21% of Type 2, and 33% of Type 3 AE patients required intubation.[16]

Treatment of AE involves steroids, antihistamines, epinephrine, and humidified oxygen. Danazol and stanazol are androgens that increase serum concentrations of C1 esterase inhibitors and can be useful in prophylactic treatment when AE episodes are possible, such as in patients with a hereditary deficiency of C1 esterase.[17] Androgenic steroids typically are used as an illicit drug and not in medical settings, but they can be effective in addressing angioedema, as seen in our patient. Fresh frozen plasma also has been utilized in treatment, but its inclusion of C4 may lead to propagation of the complement system and a worsening of AE and is reserved for prophylaxis and not acute episodes.[18]

CONCLUSIONS

Healthcare providers must be aware of AE presenting in the immediate post-operative environment. Recognition of early signs, including tongue swelling, respiratory decompensation, and difficulty speaking, may be lifesaving. Assessment of the airway and immediate intervention can prevent the mortality and morbidity associated with airway compromise.

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Keywords: angioedema, angiotensin converting enzyme inhibitor, laryngeal edema, postoperative period, airway obstruction

KANSAS JOURNAL of MEDICINE

A Unique Case of Post-Biopsy Bleeding in a Jehovah's Witness with a Rare Inherited Undetermined Coagulopathy

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Received Oct. 27, 2022; Accepted for publication Feb. 17, 2023; Published online March 15, 2023
https://doi.org/10.17161/kjm.vol16.18625

INTRODUCTION

Gastrointestinal (GI) bleeding is a common cause of hospitalization in patients with coagulopathy.[1,2] In patients with common coagulopathies such as von Willebrand Factor disease, hemophilia A, and hemophilia B, the management of bleeding with recombinant factors and hemostatic agents are well studied and outlined in the literature.[1,3,4] However, in patients with rare bleeding disorders where incidence is as low as 1-2 per million, there is not a clear consensus on management of bleeding and especially in those patients who decline blood products for religious reasons.[3-10] Management of GI bleeding is important for these patients as untreated bleeding can result in hemodynamic instability, and treatment with replacement blood and hemostatic agents can cause volume overload and the associated cardiac and renal sequelae.[3-4]

Patients with rare bleeding disorders require integrative management between primary care providers, surgeons, and hematologists for best management and prevention of bleeding events requiring hospitalization.[3,5-9] Patients also must understand their disorder, even if it is undefined, so that they may alert providers accordingly and modify their lifestyle to minimize bleeding risk. Simple interventions such as electronic health record (EHR) chart alerts and medical bracelets may improve outcomes for these patients.

In this case, a patient who was a Jehovah's Witness presented with an undefined chronic coagulopathy and two weeks of hematochezia following prostate biopsy.

CASE REPORT

A 67-year-old male who was a Jehovah's Witness presented to a local emergency department with a two-week history of hematochezia, dizziness, and fatigue following a prostate biopsy. On arrival, he was hemodynamically stable with anemia (hemoglobin (Hgb) 5.5 gm/dL) and supratherapeutic INR (2.7). Baseline Hgb measured 13 gm/dL. The patient was given oral vitamin K and transferred to our hospital for further management. Because of the patient's status as a Jehovah's Witness, he declined blood products and instead received epoetin alfa, intravenous iron, vitamin B12, ascorbic acid, and folic acid for support. The patient had no evidence of liver disease. Ultrasound of the abdomen obtained showed no ascites, biliary dilatation, or other liver abnormalities. On physical exam, the only abnormality was significant pallor.

During the interview, the patient mentioned having a bleeding disorder. However, he could not define it further and denied any active treatment for his disorder including perioperative management. Prior to proceeding with flexible sigmoidoscopy, the patient's hematology history was reviewed via a phone call with a hematology clinic nurse and revealed an undetermined chronic coagulopathy with an INR that responds to vitamin K. Also, he noted a first degree relative with a Factor V deficiency.

Flexible sigmoidoscopy revealed an adherent clot at the anal verge consistent with prostate biopsy, as well as maroon colored blood in the rectum. A clip was placed successfully without complications. Over the next several days, the anemia improved to 6.5 gm/dL. The INR decreased to 2.3 and required vitamin K; however, there were no further episodes of lower gastrointestinal bleeding. Several days after flexible sigmoidoscopy, there were new visual field deficits. Magnetic resonance imaging (MRI) brain showed no acute intracranial abnormalities, and the deficit was attributed to patient's history of macular degeneration. There were no further neurologic or bleeding events. The patient was discharged. He was advised to continue epoetin alfa, B12, and folic acid as an outpatient and to follow-up with hematology for management of supratherapeutic INR. On discharge INR was 1.1. One week following discharge from the hospital, there was further improvement in the anemia (Hgb 7.8 gm/dL) and INR increased to 1.8.

On review of the patient's coagulation history, the patient had a history of supratherapeutic INR (1.7) discovered in 2018 when hospitalized with an ischemic cerebral vascular accident. A workup at that time revealed a prolonged partial thromboplastin time (PTT; 48.2 seconds), low levels of factor II (34%), factor VII (21%), and factor IX (40%). Factor VIII level of 137% was noted with suggestion of possible inhibitor present. Workup demonstrated normal liver studies, vitamin K, and vitamin D3. A prothrombin time (PT) and PTT mixing study demonstrated correction of the PT/PTT, indicating a factor deficiency or weak inhibitor.

His coagulopathy was thought to be due to a supplement the patient was taking causing a possible vitamin K deficiency. The patient received 10 mg vitamin K by mouth daily for three days. His INR decreased to 1.2. Following this hospitalization, the patient declined hematology referral and vitamin K therapy. In 2020, the patient developed an intramuscular hematoma following a fall and he again declined hematology referral and vitamin K therapy after extensive encouragement from his primary care provider. In 2022, the patient was hospitalized with COVID-19 and had a prolonged hospitalization due to supratherapeutic INR of 4.6.

DISCUSSION

Rare bleeding disorders are named aptly due to their low incidence in the general population (1-2 per 1 million persons). Because of their rare nature, there is not standardized information in the literature on how to manage these disorders.[3,5-10] In patients with undefined bleeding disorders, management is not clear. Therefore, extensive hematologic workup and integrative management between multiple specialties is necessary. Bleeding is a common complication of these rare bleeding disorders and is of special concern in patients undergoing procedures.[3] These patients require perioperative management to prevent complications and should have a plan in place to manage bleeding even in

undefined disorders.

Although rare bleeding disorders are not common, hemophilia treatment centers have registries, and the treatments patients typically respond to have been studied.[3,5] In rare disorders, such as factor II, V, VII, dysfibrinogenemia, and afibrinogenemia, patients have seen hemostatic response to fresh frozen plasma, activated prothrombin complex concentrate/prothrombin complex concentrate, epsilon-aminocaproic acid, and recombinant factor VII.[3,5,6] However, patients who identify as Jehovah's Witnesses tend to deny blood products including packed red blood cells, plasma, fresh frozen plasma, and cryoprecipitate. The use of recombinant factors is typically acceptable in Jehovah's Witness patients; however, the use of activated prothrombin complex concentrate/prothrombin complex concentrate is accepted variably.[7] Therefore, there is even fewer hemostatic options in patients with rare bleeding disorders who are Jehovah's Witnesses.

For management of GI bleeding, current recommendations are to proceed with endoscopic hemostasis in patients with an INR of 1.5-2.5 with the use of reversal agents before or with endoscopy.[2] However, in patients with INR greater than 2.5, reversal agents should be utilized prior to endoscopic management.[1,2,9] There also has been investigation into the use of perioperative tranexamic acid plus or minus desmopressin for minimizing bleeding risk with some mild supporting evidence, however, further research is needed to know if this is a significant treatment.[1,2,9]

Because there is not a clear outline on how to manage patients with rare bleeding disorders, coordinated and extensive management needs to be undertaken by providers. Patients must demonstrate personal responsibility to inform medical personnel of a serious bleeding disorder even if it is undefined. These patients must be managed by hematologists to receive a full hemostatic workup, including identification of any factor inhibitors or acquired antibody mediated coagulopathies. Rare bleeding disorder patients should have routine lab monitoring and management to ensure sufficient factor concentrations.[3,4,6] If a hematology center is not sufficient for management, patients may be referred to hemophilia treatment centers.[6]

In aging patients, even greater care is required as these patients are at risk for thromboembolic complications and related pathologic change of vessels with age despite chronically anticoagulated blood.[3] A cross sectional analysis of cardiovascular disease in hemophilia patients demonstrated a reduced risk of cardiovascular disease in patients with hemophilia, however, more studies need to be done to confirm this risk reduction.[11] Patients with chronic bleeding disorders and cardiovascular disease need close management with cardiologists as well to balance bleeding disorder with thromboembolic risk.[3] There is also additional concern with volume overload in patients requiring frequent transfusions and reversal agents.

CONCLUSIONS

In patients with rare bleeding disorders, coordinated management is important to prevent significant bleeding events requiring hospitalization.[8-9] Although management and monitoring are not defined clearly in patients with undetermined coagulopathies, and especially those who are Jehovah's Witnesses, close follow-up and perioperative hemostatic management plans need to be in place to prevent complications. Patients also must be aware of the serious nature of their disease in events of spontaneous or provoked bleeding and must inform healthcare personnel of this issue for proper management.

Potential interventions may include EHR alerts on all patient charts with rare bleeding disorders with details of the disorder and effective hemostatic agents. Medical bracelets also may be another necessary intervention in cases where access to an EHR is not available. Although these simple interventions are likely to improve care for these patients, further genetic analysis of rare bleeding disorders and development of non-blood based hemostatic agents need to be investigated to address these concerns and provide the highest level of care in this small patient population.

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Keywords: gastrointestinal hemorrhage, Jehovah Witnesses, inherited blood coagulation disorders, coagulation protein disorders

KANSAS JOURNAL of MEDICINE

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VOLUME 16 • 2023

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