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Welcome to Our Seventh SMRJ Issue!

I’d like to welcome you to the seventh issue of The Spartan Medical Research Journal (SMRJ). As you will see in the Table of Contents, we are receiving an increasingly broader range of submissions! As noted inside the cover of this issue, the purpose of this online peer-reviewed journal is to provide an accessible formal publication option for research & QI papers and case reports from Michigan State University COM students, residents, fellows and faculty and associates. We continue to receive submissions from both Statewide Campus System affiliated and non-affiliated authors from other parts of the country and our readership continues to grow!

NOTE: All SMRJ submissions for future issue consideration will now need to be submitted using the Scholastica™ submission software. We have already received a half-dozen submissions through this mechanism and have heard no concerns regarding this change. The following link will take you directly to the new submission page through Scholastica: https://smrj.scholasticahq.com/for-authors

It is of note that our SMRJ has been online for over 24 months and as of this issue we have published exactly 60 manuscripts! As such, we have submitted an application for PubMed article number assignments and journal indexing through the US Library of Medicine. We hope to have this application reviewed in February 2019 and will keep all SMRJ authors and SCS-affiliated readers apprised of this process!

We at the SCS continue to be dependent on a large number of expert reviewers for SMRJ submissions. We are still recruiting expert reviewers from all medical specialty areas to be members of the Editorial Board. If you have an interest in participating as a reviewer, please contact Chief Editor Bill Corser.

If you have comments or suggestions, please contact any of our editorial team members at any time. Please remember that we also accept Letters to the Editor. We hope that you enjoy this issue!

Sincerely,

Bill Corser, PhD, RN, NEA-BC
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Use of Disposable Punch Biopsy Device to Add Foley Catheter Fenestration to Improve Drainage of Post Radical Prostatectomy Anastomotic Leak

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ABSTRACT

A ALLEN A, WYNBERG J, WALTON E. Use of Disposable Punch Biopsy Device to Add Foley Catheter Fenestration to Improve Drainage of Post Radical Prostatectomy Anastomotic Leak. Spartan Med. Res. J. Vol. 3, No. 3, 2019. CONTEXT: Radical prostatectomy (RP) is a major oncologic urological surgery that can have high morbidity if complications arise. Bladder-urethral urine anastomotic leaks (AL) are one of the most common complications and can greatly increase morbidity. To date, there are few resources to manage AL. One management technique is using a Foley catheter with an additional auxiliary drainage port, also known as a fenestrated catheter. This type of auxiliary drainage port allows a low-pressure drainage source that is located near the anastomosis to increase urine drainage from catheter rather than from the AL site. The optimal size and location of this additional drainage port is currently unknown. This experiment evaluated the optimal auxiliary drainage port size and an inexpensive technique to easily construct such a catheter. METHODS: Utilizing different size punch biopsies, auxiliary drainage ports were placed in different size Foley catheters and drainage rates and the structural integrity of the catheter was assessed. RESULTS: A 3.0 mm punch biopsy located 1.0 cm proximal to the Foley balloon in an 18 French (Fr) catheter was determined to be the optimal size. A 2.0 mm punch biopsy provided significantly less drainage. The 4.0 mm punch biopsy compromised the structural integrity of the catheter. CONCLUSIONS: Based on these experimental results, we recommend using a 3.0 mm punch biopsy in an 18 Fr catheter 1.0 cm. proximal to the balloon for an auxiliary drain site in Foley catheter when the anastomosis is not watertight or the surgeon has reason to believe the patient is at higher risk for an AL. Factors such as history of pelvic radiation, abnormal anatomy, large prostate, post-surgical hematoma formation, obesity, previous prostatic surgery, difficult anastomosis, blood loss and postoperative urinary tract infection may make use of this type of device more attractive. Keywords: radical prostatectomy, anastomotic leak, urine leak, fenestrated catheter

INTRODUCTION

Prostate cancer is the most common cancer in men and third most common cancer overall with 161,360 new diagnosis and 26,730 deaths in 2017. About 60,000 radical
prostatectomies (RP) are annually performed in the US. The primary indication for RP is almost always adenocarcinoma of the prostate. This oncologic surgery includes removing the prostate and seminal vesicles and suturing the bladder neck to the urethra to form the anastomosis (i.e., the connection made between the bladder and urethra).

An indwelling urethral catheter is then left in place to allow the anastomosis to heal. This anastomosis can occasionally leak urine into the tissues surrounding the bladder and is one of the most feared post-operative complications from a RP. The published rate of anastomotic leak (AL) following radical prostatectomy is 0.3 to 15.4%, meaning that approximately 180 to 9,240 prostate cancer patients in the US are annually affected by AL.

AL has been associated with multiple complications including extended hospital stays, ileus (i.e., lack of intestinal movement), infection and possibly increased risk of bladder neck contracture and/or permanent incontinence. In addition, urine is irritating to intra-abdominal organs and the peritoneal lining. If bacteria are present, the risk for infection is a significant concern that can cause sepsis, abscess formation and further tissue and organ damage. An AL is traditionally managed by an intra-abdominal drain and extended Foley catheter drainage. If a urine leak is recognized post-operatively and no drain had been left, an interventional radiology procedure to place a drain is required.

A less well-known technique includes using an intra-abdominal drain and a fenestrated Foley catheter that consists of a second drainage hole, usually placed on the other side of the inflation balloon from the standard drainage hole. Fenestrated catheters have been used for decades in the management of AL. Multiple case reports and one randomized control trial have demonstrated that fenestrated catheters can significantly reduce anastomotic leakage post-operatively. To our knowledge, there have not previously been studies evaluating the optimal size fenestration and catheter size to manage AL flow. As such the purpose of this experiment was to evaluate the optimal auxiliary drainage port size and offer an inexpensive technique to easily construct such a catheter.
METHODS

For this experiment, a Bard® 18 French (Fr) 5cc balloon Foley catheter (#0165L18) was utilized. The catheter balloon was filled with 5 ml of water to identify any compromise of balloon channel during fenestration. Care was taken to apply the punch biopsy 180 degrees from the balloon fill channel, 1.0 cm proximal to the catheter balloon. The catheter was made wet to minimize friction between punch biopsy and latex catheter. The punch biopsy was twisted and gently advanced through the lateral wall of the catheter until the catheter lumen was reached, creating a fenestration.

A sequence of 2.0 mm, 3.0 mm, and 4.0 mm Miltex® punch biopsies (2.0 mm: 33-38; 3.0 mm: 33-38; 4.0 mm: 33-38 respectively), were utilized to place a single fenestration in a Bard 18 Fr 5 cc balloon Foley catheter 1.0 cm proximal to the balloon (Figures 1-2). One fenestration was performed in two sets of catheters in order to provide two catheters for each punch size to increase the validity of the results.

A plastic bowl with a hole drilled in the bottom with Foley catheter sealed in the hole was used. (Figure 3) Waterproof tape was applied around the Foley at the base of the bowl. An S-curve was made in the Foley to ensure that any leakage around the Foley would not collect in the graduated cylinder. The authors did not observe any leaking. The new fenestration was held at a predetermined height of 18 cm to standardize the experiment for all catheters. The Foley was clamped distal to the fenestration at all times to ensure that the fluid collected was exclusively through the fenestration. Drainage commenced with filling of the bowl with water and the timer was stopped when the graduated collection cylinder reached 100 ml.

In addition to determining the rate of drainage for each respective fenestration size, the structural integrity of each Foley catheter was evaluated visually and a binary system was established classifying the 16 Fr and 18 Fr Foley catheter as having “compromised structural integrity” or “not compromised structural integrity.” (Figures 4-5) This was achieved by visually evaluating the effects of the biopsy size on the structural integrity of the system. When bending the catheter, if buckling of the catheter occurred, this was deemed to constitute compromised structural integrity of the catheter.
RESULTS

As shown in Table 1, the 3.0 mm punch biopsy hold provided superior drainage compared to a 2.0 mm punch biopsy in the 18 Fr Foley catheter. While the 4.0 mm punch biopsy provided greater rate of drainage than the 3.0 mm punch biopsy, there was greater structural compromise evident by buckling of the Foley catheter. This resulted in failure of the binary system of compromised versus not compromised structural integrity. In fact, the experimental arm using 16 Fr Foley catheter was abandoned due to an unacceptable high failure rate. The 2.0 mm and 3.0 mm punch biopsy fenestration resulted in no structural compromise of the Foley catheter.

The 3.0 mm fenestration provided more than two and a half times the rate of drainage compared to the 2.0 mm. During periods of high patient urine output, this drainage rate would be clinically significant and adequate to minimize the pressure that would increase their risk for AL.

A wide standard deviation occurred in the drainage rate of the 2.0 mm punch biopsy hole, likely due to variability in size of holes created using such a small punch biopsy and our visual observation that the 2.0 mm biopsy was small enough so that the inner lining of the catheter did not cut as smoothly as the 3.0 mm biopsy.

DISCUSSION

Prostate cancer is the most common oncologic surgery for urologists and the majority of patients who undergo surgery for prostate cancer experience treatment-related side effects. These side effects can be short term or long term, and that can significantly impact their quality of life. The portion of the surgery suturing the bladder neck to the urethra to form the anastomosis is considered the most technically challenging with urine AL at this site occurring at a rate of 0.3-15.4% of all RP cases.

Fenestrated catheters have been used for decades in management of AL urologic conditions with multiple publications to support their selective usage. To our knowledge, however, the optimal size of catheter fenestrations has not been systematically evaluated. This low pressure drainage system was first described in 1973 when Turner-Warwick used a fenestrated catheter with multiple holes to drain urethral exudate and hematoma after urethral stricture repairs and then later after pelvic fracture.
Reports as early as 2005 showed post robotic assisted laparoscopic prostatectomy (RALP) anastomotic leaks managed by replacing a standard catheter with fenestrated catheter increased the urine drainage per Foley between 1500-2120 ml/day immediately following catheter changes.\textsuperscript{5,6} This finding indicates that urine was flowing out of the catheter rather than into the extra vesical space through the leak.

The only prospective study, a 2014 randomized control trial of standard catheter vs. fenestrated catheters, showed a fenestration made 1 cm proximal to balloon had significantly less AL rates at postop Day 7. In addition, the fenestrated group had less catheter-related side effects (8/125 (6.4%) vs. 3/125 (2.4%)). Patients without leakage tended towards faster recovery of continence (68% at three months) over patients with AL (59% at three months), but this was not statistically significant (p = 0.49), perhaps due to sample size.\textsuperscript{7}

Risk factors for AL include history of pelvic radiation, abnormal anatomy, large prostate, post-surgical hematoma formation, obesity, previous prostatic surgery, difficult anastomosis, an anastomosis under tension, blood loss and postoperative urinary tract infection. Although some of these risk factors will be known preoperatively, it is often not until the surgical procedure when the anastomosis work has begun that surgeons will discover there is a less than optimal bladder-urethral anastomosis. In these situations, surgeons have limited options.

All post RP patients have an indwelling Foley catheter which allows the anastomosis to heal with minimal bladder distention reducing strain on the new anastomosis. Unfortunately, indwelling catheters are colonized by bacteria at a rate of about 5% per day; meaning by day 10, 50% of patients with an indwelling urethral catheter will have colonization in the urinary tract.\textsuperscript{10} Post RP patients normally have a catheter left in place for seven to ten days. In numerous reports, the length of time for maintaining this catheter has been found to progressively decreased from 21-30 days\textsuperscript{12} to 14-21 days\textsuperscript{13,14} and more recently to between four and seven days.\textsuperscript{15,16,17}

When an AL occurs, this urinary colonization can be catastrophic as this bacteria filled urine leaks out of the bladder. Urine is irritating to intra-abdominal organs and the peritoneal lining and if bacteria are present, the risk for infection is a significant concern that can cause sepsis, abscess formation and further tissue and organ damage.\textsuperscript{4}
One significant urologic point to emphasize is that urine leaking into the peritoneal cavity is materially different than in the extra peritoneal space. Urine is caustic and can cause peritonitis when in contact with intraperitoneal organs whereas urine in the extra peritoneal space is not generally as clinically significant. While peritonitis does not occur, complications such as infected urinomas (i.e., inflammatory response in peri-renal fat) can happen if not adequately drained. For example, a bladder perforation that leaks urine intraperitoneal must be repaired emergently whereas an extra peritoneal leak is non-operative.

One key change in urologic practice during recent years is that the majority of RP surgeries are now RALP procedures which already violate the peritoneal cavity and may allow a urine leak to enter the cavity. An open prostatectomy does not normally violate the peritoneal cavity and any leak remains extra peritoneal. A urine leak is not as clinically significant in these patients because urine does not contact the peritoneum or intra-abdominal organs and therefore there is no risk of peritonitis or ileus. AL complications are much more common in open prostatectomy, with one series from 2011-2013 showing a >50% leak rate at postoperative Day 7 on cystogram.18

Several key findings of our experiment were evident. First, it is important to use the proper size Foley catheter (18 Fr) and proper size punch biopsy (3.0 mm). Furthermore, it is essential to apply the punch biopsy to a pre-moistened Foley to minimize drag of the latex by the twisting motion of the punch biopsy. When the Foley was dry in our experiment, the punch biopsy did not easily incise the rubber surface of the catheter-the rubber twisted with the twist of the punch biopsy. Additionally, we also found it important not to compress the Foley while twisting the punch biopsy, as that increased the chances of punching through the far side inner wall and causing balloon rupture.

CONCLUSIONS

A 3.0 mm punch biopsy can be used to fenestrate a moistened 18 Fr Foley catheter on the side opposite the balloon channel 1.0 cm. proximal to the Foley balloon to increase Foley drainage. The 3.0 mm punch did not compromise the structural integrity of the 18 Fr Foley catheter. Use of punch biopsy devices larger than 3.0 mm may compromises the
structural integrity of 18 Fr catheters. The 2.0 mm punch biopsy provides lesser drainage rates and is thus considered suboptimal. This can be applied when AL occurs after radical prostatectomy and we recommend considering this method in the setting of RP with patients with a history of pelvic radiation, abnormal anatomy or a tenuous anastomosis.

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The authors declare no conflict of interest.

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Table 1
Mean Fenestrated Catheter Drainage Rate

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<th></th>
<th>2mm</th>
<th>3mm</th>
<th>4mm</th>
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<td>ml/hr.</td>
<td>2,094</td>
<td>3,605</td>
<td>9,330</td>
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<tr>
<td>SD +/-</td>
<td>747</td>
<td>307</td>
<td>484</td>
</tr>
</tbody>
</table>

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Use of Punch Biopsy to Add Fenestration to Foley Catheter to Improve Drainage

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Tranexamic Acid in the Treatment of Hip Fractures: A Clinical Review

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ABSTRACT
INTRODUCTION: Although regularly used as a method to reduce blood loss in elective orthopedic procedures (e.g., total hip and knee arthroplasty), there currently is little evidence concerning the optimal dosage, timing and route for the use of tranexamic acid to reduce postoperative blood loss in hip fracture repair. SUMMARY OF THE EVIDENCE: The current literature suggests that tranexamic acid may be used to reduce postoperative blood loss in addition to reducing the risk of requiring blood transfusions following the surgical repair of hip fractures. Furthermore, it may have the potential to improve patient outcomes and decrease the overall costs of caring for this patient population. CONCLUSIONS: Further studies are needed to truly gauge the effect of tranexamic acid on long-term patient outcomes and hospital costs. Keywords: tranexamic acid, hip fractures, blood transfusion

INTRODUCTION
There are approximately 300,000 patients annually hospitalized for hip fractures in the United States.1 As the vast majority of these injuries are treated surgically, this creates a significant burden on our healthcare system. Hip fractures are commonly associated with a relatively large amount of blood loss from the initial injury in addition to blood loss resulting from surgery.2 A range of between 20-60% of patients require blood transfusions after surgery, which may result in an increase in postoperative infections, increased length of hospital stay, and potential increases in admission costs by an average of approximately $1731.2 Serine proteases has been employed in an attempt to control postoperative hemorrhage, but with the risk of anaphylaxis, this option
was not ideal. The 2010 CRASH-2 trial tested the use of tranexamic acid (TXA), a lysine analog that has been showing promise in many aspects of orthopedics.

TXA acts as an antifibrinolytic agent by competitively inhibiting the conversion of plasminogen to plasmin, acting to minimize postoperative bleeding. Although now more regularly used as a method to reduce blood loss in elective orthopedic procedures (e.g., total hip and knee arthroplasty), there is currently little evidence concerning the optimal use (i.e., dosage, timing and route) of TXA in hip fracture repair. TXA has been thought to be a viable strategy to minimize blood loss and decrease the subsequent need for blood transfusion postoperatively. Furthermore, TXA use may improve patient outcomes by avoiding the morbidity and mortality associated with blood transfusions (e.g., allergic and hemolytic reactions, fever, etc.) and reduce the total costs of care for these patients.

SUMMARY OF THE EVIDENCE

The use of TXA in hip, knee, and shoulder arthroplasty as a way to decrease perioperative blood loss and reduce the need for postoperative blood transfusion has been well documented in the literature. There have also been studies demonstrating decreased blood loss and transfusion rates with TXA use in trauma and pelvic fractures. The current literature involving TXA use in the treatment of hip fractures is relatively sparse. Approximately 20% of all orthopedic trauma is hip fracture related. Postoperative blood loss can range from 300 to 1000 milliliters after undergoing surgical fixation secondary to over-activation of the fibrinolytic system from the initial injury in combination with the additional insult from the surgery.

TXA has been less frequently used by orthopedic surgeons in trauma procedures compared with elective procedures because of the increased activation of the fibrinolytic system and subsequent risk of venothromboembolism (VTE). VTE is defined as a condition when a blood clot forms in the venous system, typically the legs, then becomes dislodged and travels to the lungs. However, data continues to amass in support of using TXA in patients with hip fractures.

In 2017, Watts et al. examined the use of TXA in patients with acute femoral neck fractures treated with hemiarthroplasty or total hip arthroplasty.
Hemiarthroplasty is a partial hip replacement that involves replacing the proximal end of the femur and leaves the native acetabulum intact. This is in contrast to a total hip arthroplasty, which involves replacing the proximal femur in addition to placing a prosthetic cup into the acetabulum.

These authors concluded that 15 milligram/kilogram intravenous (IV) TXA given at the time of incision and just before wound closure decreased postoperative transfusion rates when compared to the control group. In 2017, Wang et al. conducted another meta-analysis that found similar results in patients with intertrochanteric hip fractures treated with dynamic hip screw or cephalomedullary nail when given IV TXA. An intertrochanteric hip fracture is an extra-capsular fracture of the proximal femur that extends obliquely from the greater to lesser trochanter. A cephalomedullary nail is a device that consists of an intramedullary rod with a lag screw that goes through the nail into the femoral head.

Drakos et al. also studied the efficacy of TXA in patients with intertrochanteric femur fractures treated with a cephalomedullary nail and noticed a 43% reduction in the number of transfusions in patients who received TXA. These patients received 3.0 grams of TXA injected under the deep fascia near the fracture site. For those patients who required blood transfusions, they received fewer units of blood compared to the control group. This study group also found the use of TXA to be cost effective, saving the hospital 77 euros (89.14 USD) per patient.

Another concern with hip fractures is the phenomenon of “hidden blood loss.” The amount of hidden blood loss depends on the severity of the injury and the treatment, whether it be cannulated screws, dynamic hip screw, cephalomedullary nail, or arthroplasty. In 2018, Lei et al. demonstrated that patients treated with a cephalomedullary nail who received 1.0 gram of IV TXA prior to incision had an average lower hidden blood loss of 210 milliliters compared to the control group, which had 359 milliliters. Additionally, they noted that the transfusion rates decreased approximately 50% in those who received TXA.

This is in contrast to a 2016 study by Viriani et al., that found no statistically significant difference in average postoperative blood loss or hemoglobin levels when 2.0 grams of TXA was administered at the fracture site in patients treated with dynamic hip
screw and barrel plating.\textsuperscript{17} This study remains one of the few in which TXA has not shown to be beneficial. This may be related to the conclusion that an increase in inflammatory markers, specifically the acute phase protein alpha-1 acid glycoprotein, is higher in this population of patients and may negate the use of TXA.\textsuperscript{19}

In 2018, Schiavone et al. showed that patients with intertrochanteric femur fractures had a decrease in the percentage of hemoglobin lost postoperatively, although not a statistically significant difference in decreased transfusion rates when administered IV TXA.\textsuperscript{18} The group also noted that TXA use in their sample patients with intertrochanteric femur fractures experienced an increase in VTE, although these findings were not statistically significant.\textsuperscript{18} Tenberg et al. (2016) treated intertrochanteric femur fractures with cephalomedullary nails and administered 1.0 gram of IV TXA preoperatively and 3.0 grams of IV TXA postoperatively.\textsuperscript{19} These authors noted a mean blood loss reduction of 570 milliliters compared to 2100 milliliters in patients who had not received TXA. Of note, this study did show an increase in the 90-day mortality rate in the experimental group, although the increase was not quite statistically significant, $p = 0.07$.\textsuperscript{19}

A 2016 study by Baruah et al. demonstrated decreased postoperative total blood loss in intertrochanteric hip fractures fixed with dynamic hip screws when given a single dose of 15 milligram/kilogram IV TXA fifteen minutes prior to surgery.\textsuperscript{20} The authors noted that there were no VTE events in either the control group or experimental group patients who received TXA.\textsuperscript{20} Similar results were found in another randomized controlled trial including 271 patients with femoral neck fractures managed with hemiarthroplasty.\textsuperscript{21} These patients were given a 1.0 gram preoperative IV bolus of TXA and found to have decreased total blood loss and decreased transfusion rates. Additionally, they identified no difference in 30 or 90-day mortality between the TXA and control groups.\textsuperscript{21}

In 2015, Mohib et al. conducted an observational cohort study of 100 patients with hip fractures.\textsuperscript{22} These patients were given two IV dosages of 15 milligram/kilogram TXA, one before incision and one three hours after the initial dosage. The patients treated with TXA had a mean postoperative hemoglobin of 10.2 grams/deciliter compared to the mean of 8.9 grams/deciliter in the control group ($p = 0.007$). There was
also a 42% reduction in the transfusion rate in those patients receiving TXA \((p = 0.009)\).^{22}

TXA is typically well tolerated in patients. However, the optimal dosing regimen has not yet been clearly defined in the literature, with regards to timing and route of administration.\(^1\) Absolute contraindications to TXA include allergy to TXA as well as a concurrent subarachnoid hemorrhage.\(^{10}\) The use of IV TXA in patients with a history of VTE or PE, ischemic TIA, acute MI, or known seizure disorder is relatively contraindicated.\(^{23-25}\)

**CONCLUSIONS**

Hip fractures continue to place a significant healthcare cost burden on our healthcare system. Much attention has been placed on the timing and type of surgical intervention in these patients, as well as an overall team approach to managing them. However, with rising life expectancy and an increased number of people living with chronic health conditions, the prevalence of hip fractures will continue to rise. The benefits of TXA in elective hip and knee arthroplasty, as well as the general trauma literature are well documented, and its use has become a standard at most institutions. Despite this, the use of TXA is not as widely utilized in the hip fracture population due to the concerns of possible increased risk of VTE.

This clinical review examined much of the current data involving TXA in the hip fracture population. The majority of the current literature supports the use of TXA in patients with hip fractures, with evidence generally suggesting decreased transfusion rates and blood loss in these patients. However, unlike elective hip and knee arthroplasty patients, hip fracture patients are a less controlled group. These are frequently not elective surgeries and as a result, they are often a higher risk population for perioperative morbidity and mortality.\(^1\)

Furthermore, hip fracture patients experience a double-insult of blood loss, both from the initial fracture, as well as the surgical intervention.\(^2\) This makes it more difficult to evaluate the efficacy of TXA in these patients, as timing of TXA administration is paramount and well established in the general trauma literature. Further randomized controlled trials are needed to help define the optimal timing and route of TXA use in
varied types of hip fracture patients. These studies could further investigate TXA administration in this population within an established window of the sentinel event injury, as well as perioperatively.

The current literature is encouraging, and generally supports the use of TXA in hip fracture patients without contraindications. As orthopedic surgeons will continue to strive to decrease the significant morbidity and mortality seen in the hip fracture population, TXA appears to be a safe and effective medication to decrease both postoperative blood loss and minimize blood transfusions after hip fracture surgery.

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The authors declare no conflict of interest.

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REFERENCES


TABLE AND FIGURES

Figure 1
Box Summary

Clinical Question:
What role does tranexamic acid have in the treatment of hip fractures?

Current Evidence:
The current literature suggests that tranexamic acid may be used to reduce postoperative blood loss in addition to reducing the risk of requiring blood transfusions following the surgical treatment of hip fractures. Furthermore, it may have the potential to improve patient outcomes and decrease the overall costs of caring for this patient population.

Take Home Message:
The current literature supports the use of tranexamic acid in the treatment of hip fractures in patients without the known contraindications. Further studies are needed to truly define its effect on long-term outcomes and hospital costs.
Table 1
Recent Studies on TXA Use in the Surgical Treatment of Hip Fractures

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Hip Fracture</th>
<th>Blood Loss</th>
<th>Blood Transfusion</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watts et al. 2017</td>
<td>RCT with 138 patients</td>
<td>Arthroplasty for femoral neck fracture</td>
<td>Reduced by 305 mL in TXA group (p=0.0005)</td>
<td>Reduced by 9% in TXA group (p=0.22)</td>
<td>No increased risk with TXA</td>
</tr>
<tr>
<td>Drakos et al. 2017</td>
<td>RCT with 200 patients</td>
<td>IT fracture treated with DHS or CMN</td>
<td>Reduced HCT loss by 2.5 in TXA group (p&lt;0.01)</td>
<td>Reduced by 43% in TXA group (p&lt;0.01)</td>
<td>No increased risk with TXA</td>
</tr>
<tr>
<td>Virani et al. 2016</td>
<td>RCT with 137 patients</td>
<td>IT fracture treated with CMN</td>
<td>No significant difference in blood loss</td>
<td>No significant difference in transfusion rate</td>
<td>No increased risk with TXA</td>
</tr>
<tr>
<td>Schiavone et al. 2018</td>
<td>RCT with 90 patients</td>
<td>IT fracture treated with CMN</td>
<td>n/a</td>
<td>Reduced by 18% in TXA group (p&lt;0.05)</td>
<td>No increased risk with TXA</td>
</tr>
<tr>
<td>Tengberg et al. 2016</td>
<td>RCT with 72 patients</td>
<td>IT fracture treated with CMN</td>
<td>Reduced by 570 mL in TXA group (p=0.029)</td>
<td>Reduced by 0.6% in TXA group (p=0.21)</td>
<td>No increased risk with TXA</td>
</tr>
<tr>
<td>Barauh et al. 2016</td>
<td>RCT with 60 patients</td>
<td>IT fracture treated with DHS</td>
<td>Reduced by 270 mL in TXA group (p&lt;0.001)</td>
<td>n/a</td>
<td>No increased risk with TXA</td>
</tr>
<tr>
<td>Lee et al. 2015</td>
<td>Retrospective cohort study of 271 patients</td>
<td>Hemiarthroplasty for femoral neck fractures</td>
<td>Reduced drop in hemoglobin (&lt;2g/dl) in TXA group (p=0.014)</td>
<td>Reduced by 13% in TXA group (p=0.005)</td>
<td>No increased risk with TXA</td>
</tr>
<tr>
<td>Mohib et al. 2015</td>
<td>RCT with 100 patients</td>
<td>IT fractures treated with DHS or CMN</td>
<td>Reduced hemoglobin loss by 1.3 g/dl in TXA group (p=0.007)</td>
<td>Reduced by 24% in TXA group (p=0.009)</td>
<td>No increased risk with TXA</td>
</tr>
</tbody>
</table>

RCT: Randomized Controlled Trial
IT: Intertrochanteric
DHS: Dynamic Hip Screw
CMN: Cephalomedullary nail
TXA: Tranexamic Acid
n/a: not available
Statistical significance: p<0.05
Systematic Review of the Effects of Phosphodiesterase-5 Inhibitors and Dexamethasone on High Altitude Pulmonary Edema (HAPE)

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ABSTRACT

AMY BLISS A, MAHAJAN S, BOEHM K. Systematic Review of the Effects of Phosphodiesterase-5 Inhibitors and Dexamethasone on High Altitude Pulmonary Edema (HAPE). Spartan Med. Res. J. Vol. 3, No. 3, 2019. OBJECTIVE: To review and synthesize the current available evidence of the effects of phosphodiesterase-5 inhibitors and dexamethasone on the outcomes of individuals affected by acute mountain sickness symptoms and High Altitude Pulmonary Edema (HAPE). METHODS: In 2015, two authors independently performed separate searches using three different databases (PubMed, Ovid and Web of Science) later reviewed by the third author. The searches used the following terms “High Altitude Pulmonary Edema” and “Phosphodiesterase-5 Inhibitors” while the second search used “High Altitude Pulmonary Edema” and “Dexamethasone”. The following exclusion criteria were utilized: patients < 18 years old, non-human studies, studies at altitudes < 2,000 meters. The search included articles from year 2000 to current. RESULTS: A total of 237 manuscripts were initially reviewed. The search involving phosphodiesterase-5 inhibitors initially yielded 37 manuscripts, four of which met inclusion criteria. A total of 101 patients were included in these articles. For the Dexamethasone search, 200 manuscripts were retrieved. Three of these studies met the inclusion criteria, reporting data on a total of 66 patients. None of the studies reported significant improvements in outcomes of patients from the use of either phosphodiesterase-5 inhibitors or dexamethasone. CONCLUSIONS: According to the current available literature, neither phosphodiesterase -5 inhibitors or dexamethasone significantly alter the outcome of individuals affected by HAPE. Keywords: acute mountain sickness, high altitude pulmonary edema, phosphodiesterase-5 inhibitors, dexamethasone

INTRODUCTION

Areas with high altitude are becoming more and more common as destinations for people traveling for business and/or pleasure. High altitude pulmonary edema (HAPE) is
a potentially life-threatening, non-cardiac, pulmonary edema that affects otherwise healthy individuals at high elevations; specifically altitudes of 2,000 meters and greater.\(^1\) The prevalence of altitude sickness, more specifically Acute Mountain Sickness (AMS) has relatively recently been observed at levels as high as 36.7\(^\%\) \(^2\) and 34.0\(^\%\).\(^3\) On average, about 40 million people travel to elevations in the US that put them at risk for developing different AMS symptoms along the high altitude sickness spectrum, including HAPE.\(^4\) In addition, an increasing number of people are traveling to elevations greater than 4000 meters around the world.\(^4\) Consequently physicians, specifically emergency medicine physicians, may encounter any part of the spectrum of AMS conditions with increasing frequency.

HAPE is at the more severe end of the altitude illness spectrum and the leading cause of death from altitude illness.\(^5\) It is a non-cardiogenic pulmonary edema with a multi-factorial pathophysiology with pulmonary hypertension at the cornerstone of its mechanism.\(^4\) Auerbach described the typical cascade of HAPE as follows: The higher a person ascends up a mountain, there is a lower arterial partial pressure of oxygen. This causes hypoxic pulmonary vasoconstriction that will cause an increase in pulmonary hypertension. This results in over perfusion of the lungs that causes a vicious cycle of pulmonary and peripheral venous constriction that in turn causes an increase in pulmonary blood volume. As this continues, there is an increase in capillary pressure that will eventually cause capillary leak, thus decreasing alveolar sodium and water clearance, resulting in HAPE.\(^4\)

The management of HAPE is aimed at both prevention and treatment. Prevention involves acclimatization and controlled ascent, which helps to maintain consistent oxygen delivery to tissues.\(^6\) Additionally, acetazolamide, a carbonic anhydrase inhibitor, has been used to help prevent HAPE. The gold standard treatment for HAPE is rapid descent. Not every situation permits rapid descent, however, so other options for treatments include oxygen supplementation and pharmacotherapy. This review focuses on two medications in particular. The first medication, dexamethasone, stimulates alveolar sodium and water reabsorption and enhances nitric oxide availability in pulmonary vessels.\(^7\) The second class of medications are phosphodiesterase-5 inhibitors, which enhances pulmonary
vasodilation. The purpose of this paper is to review and synthesize the current available evidence of the effects of these two medications on HAPE and AMS symptoms.

**MATERIALS AND METHODS**

The first two authors independently searched three different databases: PubMed, Ovid Medline and Web of Science. The first author used the following terms “High Altitude Pulmonary Edema” and “Phosphodiesterase-5 Inhibitors” in each of the databases. The second author searched for results using the following, “High Altitude Pulmonary Edema” and “Dexamethasone” in the same databases. The results of the searches were reviewed by both of the authors and later reviewed by the third author. The authors then reviewed the title, abstract, and full-text reviews and abstracted data from the studies.

The following exclusion criteria were utilized: patient < 18 years old, non-human studies, altitudes < 2,000 meters (m) studies. The search included articles from year 2000 to current as there were no reports of HAPE and Phosphodiesterase-5 Inhibitors prior to 2000. Only randomized controlled trials that reported human data on the effects of these two medications were included. These exclusion criteria were selected to ensure only adult, human studies were analyzed in our study as HAPE does not occur in altitudes of under 2,000 m.

The same two authors independently reviewed the eligible studies and extracted data on study objectives, number of subjects, interventions, comparisons, and relevant outcomes. The third author reviewed these findings. The results of each study were examined and compiled into tables.

**RESULTS**

The search terms initially yielded a total of 237 manuscripts were retrieved initially with all search terms. The “phosphodiesterase-5 inhibitors” and “high altitude pulmonary edema” search initially yielded 37 manuscripts, four of which met inclusion criteria and were randomized controlled trials. Two of the six papers examined the effects phosphodiesterase-5 inhibitors as well as dexamethasone. A total of N = 101 patients were included across these articles. The search using “dexamethasone” and “high altitude pulmonary edema,” initially generated 200 titles. Three of these studies met the inclusion criteria, reporting data on N = 66 subjects (Figure 1).
Summary of Phosphodiesterase-5 Inhibitors Studies

The first 2006 study reviewed was conducted by Hsu et al. This study examined the effects of 5-phosphodiesterase (5-PDE) inhibitor, sildenafil, during normoxic (i.e., normal oxygen concentration) exercise and during exercise at simulated high altitude conditions causing hypoxic exercise. The study involved 11 healthy, non-smoking male cyclists and triathletes ages 18-35 who volunteered for the study; one withdrew during testing. A total of 10 men performed one practice and three experimental trials at sea level and simulated high altitude of 3,874 m (subjects breathed 12.8% oxygen). Double-blinded capsules (placebo, 50mg sildenafil, or 100mg sildenafil) were given one hour before exercise. For the high altitude trials, subjects began breathing the hypoxic gas for one hour prior to exercise. They found that sildenafil had no effects on any cardiovascular or performance measures had no effects while at high altitude, although sildenafil increased stroke volume, cardiac output and SaO2. No dose response effects were observed. A post hoc analysis compared sildenafil responders versus non-responders. This study found that sildenafil can significantly improve cardiovascular function while cycling in an acute hypoxic environment.

The second study reviewed was completed in 2005 by Ricart, et al. It examined the effects of the 5-phosphodiesterase (5-PDE) inhibitor, sildenafil, on pulmonary arterial pressure as well as oxygen transport and cardiopulmonary parameters in humans during exposure to hypobaric hypoxia at rest and after exercise. In this double-blind study, 100 mg sildenafil or placebo was administered orally to 14 healthy volunteers 45 minutes before exposure to simulated altitude of 5,000 m. Arterial oxygen saturation, heart rate, tidal volume, respiratory rate, left ventricular ejection fraction, and pulmonary arterial pressure were measured first at rest in normoxia, at rest and immediately after exercise during hypoxia, and after exercise in normoxia. Measurements of the effect of sildenafil on exercise capacity during hypoxia did not provide conclusive data, although it was noted...
that sildenafil diminished pulmonary hypertension induced by exposure to hypobaric hypoxia at rest and after exertion.⁹

An additional 2009 study by Lalande et al. set out to determine the effects of acetazolamide and sildenafil on ventilatory control and breathing efficiency during submaximal steady-state hypoxic exercise in a sample of 15 healthy individuals. Following 18 hours of hypoxic exposure in an altitude tent at an oxygen concentration of 12.5% (simulated altitude of 4,300 m), participants performed 10 minutes of hypoxic exercise on a stationary bicycle at 40% of their sea level peak oxygen uptake (VO₂) while randomly receiving sildenafil 40 mg, acetazolamide 125 mg, or a placebo. There was no difference in VO₂ during exercise between conditions while subgroup SaO₂ levels were greater with acetazolamide compared to both placebo and sildenafil. Acetazolamide increased ventilation and reduced end tidal carbon dioxide (CO₂) compared to placebo and sildenafil. Breathing was less efficient with acetazolamide in comparison to placebo and sildenafil, while sildenafil did not change VE/VCO₂ during hypoxic exercise. Specifically, researchers found that sildenafil decreases pulmonary hypertension when subjects are exposed to acute hypoxia.¹⁰

The final 2011 study involving phosphodiesterase-5 inhibitors that was reviewed was performed by Bates et al.¹¹ This study examined the effect of chronic sildenafil administration on pulmonary artery systolic pressure and symptoms of AMS during acclimatization to high altitude. Sixty-two healthy volunteers were flown to La Paz, Bolivia (3,650 m), and after four-to-five days of acclimatization, they ascended over 90 minutes to 5,200 m. The treatment group (N = 20) received 50 mg sildenafil citrate three times daily. Pulmonary artery systolic pressure (PASP) was recorded by echocardiography at sea level and within six hours, three days, and one week at 5,200 m. There was no significant difference in PASP at 5,200 m between sildenafil and placebo groups. Sildenafil administration did not affect pulmonary artery systolic pressure in healthy lowland subjects at 5200 m but AMS symptoms were significantly more severe on Day 2 at 5,200 m with sildenafil. Ultimately, the data examined in this paper did not support the prophylactic use of sildenafil.¹¹
Summary of Dexamethasone Studies

In the search utilizing the terms “dexamethasone” and “high altitude pulmonary edema”, the first 2006 study by Maggiorini et al. compared dexamethasone and tadalafil with placebo to ascertain reduction in the incidence of HAPE and AMS symptoms in those adults with a history of HAPE. This was a randomized, double blind, placebo controlled study with 29 patients. Patients were randomized to receive prophylactic tadalafil (10 mg), dexamethasone (8 mg), or placebo twice a day during ascent and stay at 4,559 m. Ascent was from 490 m within 24 hours and the stay at 4,559 m was for two days. HAPE was diagnosed with chest x-ray findings (score > 1/infiltrate or alveolar edema in one or more lung fields) and the presence of AMS was defined as a Lake Louise Score > 4.

Doppler echo was used to measure systolic artery pressure and nasal potentials were measured as a surrogate marker of alveolar sodium transport. Two participants who received tadalafil developed severe AMS symptoms on arrival at 4,559 m and withdrew from the study (no signs of HAPE at this time). HAPE developed in seven of nine participants in the placebo subgroup, one in eight in the tadalafil subgroup, but none in the dexamethasone subgroup. Systolic pulmonary artery pressure was increased less in those receiving dexamethasone and tadalafil, than those on placebo. This showed improved response to dexamethasone for HAPE treatment.

The second 2009 study reviewed was conducted by Fischler et al. This study examined 23 subjects with previous HAPE, randomized to receive Dexamethasone 8 mg twice daily, Tadalafil 10mg twice daily, and placebo prior to ascent. Baseline cardiopulmonary exercise test (CPET) and echo were performed at 490 m, two-to-four weeks before ascent to 4,559 m. Subjects were taken by cable car from 1,100 m to 3,200 m, from where they continued by foot for approximately 1.5 hours until they reached 3,650 m. After an overnight stay, the study participants climbed under professional guidance within four-to-five hours to 4,559 m, where CPET was performed four-six hours after arrival and echo was performed on the following day.

The study’s results indicated that compared with placebo, dexamethasone improved maximum oxygen uptake, oxygen kinetics, and reduced the ventilator equivalent for CO2. Dexamethasone improved exercise capacity, oxygen uptake kinetics and limited hypoxia-induced pulmonary hypertension at 4,559 m in HAPE-susceptible
individuals, whereas tadalafil did not significantly improve exercise capacity and somewhat less-limited hypoxia-induced pulmonary hypertension. Peak oxygen saturation did not differ significantly between the three study subgroups. Pressure gradient over TV (indirect measure of PA pressure) was significantly less for both dexamethasone and tadalafil compared to placebo.

AMS levels improved significantly in the dexamethasone group. Peak exercise capacity decreased in all groups however with the smallest decrease in the dexamethasone group. Overall, dexamethasone was shown to be superior in controlling symptoms and incidence of HAPE compared to both placebo and tadalafil.12

This was further assessed by Siebenmann et al.,13 who extended the study design to include up to five days. Twenty-four subjects with previous HAPE exposure were included. They traveled to 1,205 m by cable car then continued by foot to 3,647 m where they arrived in the late afternoon and spent the night. The next morning, they made their ascent to 4,559 m. They stayed there for five days. All these individuals were evaluated on bicycle ergometers at an altitude of 490 m (two-three weeks before) and at 24 hours after rapid ascent to 4,559 m.

Maximal workload, heart rate, minute ventilation, calculated maximal voluntary ventilation, respiratory frequency, tidal volume, respiratory exchange ratio, and arterial oxygen saturation were measured. Results indicated that at 4,559 m, maximal oxygen uptake was higher in the dexamethasone group compared to control. Dexamethasone reduced the hypoxia related decline in maximum oxygen uptake. Dexamethasone also reduced AMS symptoms compared to control group patients.13

**DISCUSSION/LIMITATIONS**

When considering the proposed mechanism for HAPE, immediate descent appears to be the best treatment of choice. By decreasing altitude, there will be an increase in the percentage of oxygen available, thus increasing the PaO2, decreasing the altitude hypoxia, and changing the rest of the negative cascade that follows. The phosphodiesterase-5 inhibitors reduce pulmonary and peripheral venous constriction thus countering the increase in capillary pressures that occur on the cascade, thus complete preventing HAPE. Dexamethasone works on the portion of the cascade that
causes capillary leak, increasing the sodium in the alveoli and increasing water reabsorption further down the cascade.\textsuperscript{4}

This systematic review examined the current available literature on the effects of phosphodiesterase-5 inhibitors and dexamethasone on physiologic variables associated with HAPE. Overall, the studies involving phosphodiesterase-5 inhibitors had small sample sizes. Hsu et al.\textsuperscript{8} only had a sample size of ten while Bates et al.\textsuperscript{11} examined the largest number of subjects with a sample size of 62. Each study measured different physiologic variables including but not limited to pulmonary artery pressure, stroke volume, cardiac output, ventilatory control, breathing efficiency, and arterial oxygen saturation. Additionally, three of the studies simulated high altitude and/or hypoxia while only one tested subjects in the field at an actual high altitude.\textsuperscript{8-11}

Also, both simulated and actual elevations differed from 4,300 m to 5,200 m, a difference of almost 1,000 m. The effects of two different phosphodiesterase-5 inhibitors were investigated in the different papers: sildenafil and tadalafil. The differences in variables examined and methods create difficulty in comparing the results of these studies. Overall, the studies included in the review that examined phosphodiesterase-5 inhibitors did show some changes in physiologic variables but the overall impact of these medications on outcomes of individuals with HAPE was not examined.

After reviewing the results of these studies, it may be postulated that, given the mechanism of action of phosphodiesterase-5 inhibitors, it could improve outcomes in patients with HAPE. However, there is no current conclusive evidence that this is correct. Additionally, there are many unknown factors pertaining to each individual patient, specifically pharmacogenomics. The authors believe that the challenges of further research would be difficult since HAPE is so multifactorial as already indicated and environmental in nature.

To better study HAPE, one suggestion would be to conduct a larger randomized trial at a fixed location (e.g., base camp at Everest) for a longer period of time to separately test the effects of these types of medications. With the popularity of mountaineering increasing, we believe that there will likely be more opportunities for studies in base camps around the world. Additionally, there will be more diversity within the subjects included in analytic samples.
Three papers which examined the use of dexamethasone and its effects on high altitude pulmonary edema were reviewed for this systematic review. Unfortunately, the sample sizes in each of these papers were small, ranging from 23 to 29. Two of the papers compared dexamethasone to tadalafil \(^7,^{12}\) while only one examined dexamethasone alone.\(^{13}\) Again, these papers examined different physiologic variables including pulmonary artery pressure, VO2 max, and oxygen saturation, making comparison of data difficult. In general, the studies involving dexamethasone that were reviewed demonstrated improved physiology at high altitude when compared to a placebo.

**CONCLUSIONS**

Each year, there has been an increasing number of people traveling to high altitudes.\(^4\) Although there is an exhilarating thrill behind such forms of recreation, there is also a risk of exposing self to various forms of AMS and HAPE. On the extreme end of this AMS illness spectrum is HAPE, which can prove life threatening. In an ideal situation, the best treatment option appears to be immediate descent. However, in certain circumstances, this may not be a feasible immediate option.

Alternately, the use of pharmacotherapy to allay AMS and HAPE symptoms until descent is possible offers temporizing methods to decrease significant morbidity and mortality. Although our review of the literature in this area provides some insight on available treatment options, further studies examining the specific effects of phosphodiesterase-5-inhibitors and dexamethasone are warranted.

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The authors declare no conflict of interest.

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REFERENCES


Figure 1
Article Eligibility Criteria

Records identified through electronic database searching (n=237)

- Records including “Phosphodiesterase-5 Inhibitors” and “High Altitude Pulmonary Edema” (n=37)
- Records including “Dexamethasone” and “High Altitude Pulmonary Edema” (n=200)

Exclusion Criteria:
1. Pt < 18 years old
2. Nonhuman studies
3. Altitude < 2000m

- Randomized controlled trials from the year 2000 to current that met inclusion criteria (n=4)
- Randomized controlled trials from the year 2000 to current that met inclusion criteria (n=3)
## Table 1
### Summary of Sildenafil Articles Reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Relevant Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu et al. (2006)</td>
<td>10</td>
<td>Healthy, non-smoking male cyclists and triathletes</td>
<td>Sildenafil</td>
<td>At sea level vs simulated high altitude</td>
<td>At high altitude, sildenafil increased stroke volume, cardiac output and SaO2</td>
</tr>
<tr>
<td>Ricard et al. (2005)</td>
<td>14</td>
<td>Healthy males who normally live at sea level</td>
<td>Sildenafil</td>
<td>Hypobaric hypoxia at rest and after exercise</td>
<td>Sildenafil diminishes pulmonary hypertension induced acute exposure to hypobaric hypoxia at rest and after exercise</td>
</tr>
<tr>
<td>Lalande et al. (2009)</td>
<td>15</td>
<td>Healthy males and females</td>
<td>Sildenafil</td>
<td>Sildenafil vs acetazolamide vs placebo all at simulated altitude of 4,300 m</td>
<td>Sildenafil did not affect breathing efficiency</td>
</tr>
<tr>
<td>Bates et al. (2011)</td>
<td>62</td>
<td>Healthy males and females</td>
<td>Sildenafil</td>
<td>The difference in pulmonary artery systolic pressure at high altitude with sildenafil vs placebo</td>
<td>There was no significant difference in pulmonary artery systolic pressure at high altitude between the sildenafil and placebo groups</td>
</tr>
</tbody>
</table>
### Table 2
Summary of Dexamethasone Articles Reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Relevant Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maggiorini et al. (2006)</td>
<td>29</td>
<td>Adults with previous HAPE</td>
<td>Tadalafil and</td>
<td>Tadalafil vs dexamethasone vs placebo to ascertain reduced incidence of HAPE and AMS in those with previous hx of HAPE</td>
<td>Both dexamethasone and tadalafil decrease systolic pulmonary artery pressure and may reduce incidence of HAPE. Dexamethasone also helps to reduce incidence of AMS in these individuals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dexamethasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fischler et al. (2009)</td>
<td>23</td>
<td>Subjects with hx of previous HAPE</td>
<td>Tadalafil and</td>
<td>Dex vs tadalafil for improving exercise capacity (by reducing hypoxia induced pulmonary vasoconstriction)</td>
<td>Dexamethasone may improve exercise capacity during hypoxia in HAPE-susceptible mountaineers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dexamethasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siebenmann et al. (2011)</td>
<td>24</td>
<td>HAPE susceptible individuals</td>
<td>Dexamethasone</td>
<td>Placebo vs dexamethasone for maximal oxygen uptake at high altitudes</td>
<td>Dexamethasone prophylaxis increase maximal oxygen update (generally reduced due to hypoxia) of HAPE-susceptible individuals for prolonged period of time, without affecting arterial oxygen saturation at maximal exercise</td>
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Comparative Evaluation of Two Obstetrical/Gynecology Resident “Boot Camps” of Different Lengths: Equivalent Practice Skills Confidence and Knowledge Levels

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ABSTRACT

POSTLEWAITE JD, BOES D, FINAZZO S, CANTRELL C, CORSER WD. Comparative Evaluation of Two Obstetrical/Gynecology Resident “Boot Camps” of Different Lengths: Equivalent Practice Skills Confidence and Knowledge Levels. Spartan Med. Res. J. Vol. 3, No. 3, 2019. CONTEXT: Since the earlier time of master-apprentice type GME relationships, more residency program educators have developed various forms of boot camps to ease incoming learners into their new specialty roles as first-year residents. Such boot camps have ranged from informal informational sessions with faculty using simulation activities, to more formal workshops entailing pre- and post-event skills assessments with simulation exercises, formative feedback and debriefing sessions. The purpose of this pilot project was to examine for relative pre- and post-boot camp changes in Obstetrics/Gynecology (OB/GYN) practice skills confidence and knowledge levels in two consecutive cohorts (2014 and 2015) of first-year residents. METHODS: Boot camps were of two different lengths: a five-day 2014 camp (n = 32 residents) and shortened three-day 2015 boot camp (n = 29 residents). Respondents from both boot camp cohorts were invited to complete the same 25-item OB/GYN practice skills confidence and knowledge survey. The first three authors developed this survey prior to the initial boot camp (2014). Revisions/adjustments were then made to content after the 2014 to pare down from the initial five days’ worth of content for the 2014 boot camp to three days for the 2015 boot camp. RESULTS: Each of 45 sample resident respondents who provided complete pre- and post-boot camp data demonstrated improvements in self-rated practice confidence and knowledge levels. Mean per resident pre-post-boot camp survey rating levels for individual items in the shorter 2015 boot camp cohort increased by 1.096 (SD = 0.5487), over a two-fold increase for most individual items in the 2014 residents. Mean cohort differences represented a non-significant equivalent increase in pre-post practice confidence and knowledge levels for individual ratings items between the 2014 and 2015 cohorts (p = 0.241). CONCLUSIONS: Based on these preliminary results, the authors conclude that it may be possible to adjust their OB/GYN boot camp from five days to three and still achieve comparable learner outcomes while delivering the same basic content. Keywords: resident boot camps, OB/GYN, practice confidence, knowledge improvements
INTRODUCTION

Throughout their undergraduate and postgraduate medical education as learners, most incoming resident physicians face a series of transitions that can be stressful, sometimes causing them to question the adequacy of their clinical skills as they enter graduate medical education (GME) training. The major transition entailed from completing a medical school program to starting a specialty residency program may cause many new residents to experience uncertainty or anxiety concerning their preparation to enter clinical practice.1-3

Since the earlier time of predominant master-apprentice type GME relationships, more residency program educators have developed various forms of boot camps to ease incoming resident learners into their new/prospective specialty roles as first-year residents.1,3-12 As has been noted in one meta-analysis, one proposed definition is “A boot camp is a focused course designed to enhance learning, orientation, and preparation for learners entering a new clinical role.”11

To date, boot camps have ranged from informal informational sessions with faculty, using some types of simulation activities, to more formal workshops entailing pre and post-event needs and skill assessments with simulation exercises, formative feedback and debriefing sessions.10-13 Although the development and delivery of simulation-based boot camp sessions has increased, there continues to be a relative shortage of published studies which have systematically evaluated how various boot camp formats might be associated with GME learner outcomes.4,6,8,10,11

For over 25 years, the Statewide Campus System 14 (SCS) in the Michigan State University College of Osteopathic Medicine has coordinated the educational offerings for resident physicians and faculty across the state. The SCS currently serves over 190 community-based residency programs in 37 affiliated healthcare systems. In 2014, the SCS-affiliated clinician authors of this paper (JDP, DB, SF) initiated a five-day Obstetrics & Gynecology (OB/GYN) skills and competency boot camp in an effort to better prepare a sample of 32 first-year resident learners from 13 osteopathic-oriented Michigan programs.

Although the feedback from the first 2014 boot camp participants was positive, the OB/GYN authors (JDP, DB, SF) felt that it may be prudent to shorten the 2015 boot camp
based on the logistical (e.g., resident and faculty schedules, venue costs, etc.) complexities of delivering the longer event for learners from across the state. After reviewing the boot camp content, it was determined they could cover the same content in three days specifically by minimizing content duplication.

**Purpose of Analyses**

The purpose of these exploratory descriptive analyses was to examine for relative pre and post-boot camp changes in OB/GYN practice skills confidence and knowledge ratings in two cohorts of first-year OB/GYN residents post completion of boot camps of two different lengths: either a five-day boot camp (July, 2014) or a shortened three-day boot camp (July, 2015).

**METHODS**

The first 2014 boot camp was established by the first four authors (JDP, DB, SF, CC) to run for five consecutive days for first-year incoming residents from one of 13 OB/GYN Osteopathic Residencies in Michigan. The number of first-year residents in each residency program ranged between two and four, and the SCS provided a mechanism (website calendar downloadable pdf’s) to share OB/GYN pre-boot camp educational resources.

The 2014 boot camp was structured to encompass an introduction to technical OB/GYN practice skills and knowledge content to help residents develop confidence in the transition from medical school to residency. Because our incoming resident learners come from around the country, it also allowed the residents to self-assess how confident they felt in their OB/GYN practice skills and knowledge compared to their colleagues from different medical school backgrounds.

This 2014 five-day boot camp encompassed didactic presentations, various knot tying skills, episiotomy/perineal laceration repair, a variety of obstetrical skills (with a full day in the campus-based simulation center), OB/GYN triage cases, and quality and safety in the hospital. There was intentional repetition with some of the planned skills training to encourage retention. Fetal heart rate (FHR) interpretation was also a component of this boot camp. In 2015, the authors had decided to consolidate most of the same basic
content into a three-day boot camp. Participation in both boot camps was encouraged but not mandatory.

Respondents from both the 2014 and 2015 boot camp cohorts were invited to complete the same 25-item OB/GYN practice skills confidence and knowledge survey that had been developed by the first three authors (JDP, DB, SF) before the first 2014 boot camp. (Appendix 1) The survey items each used a 1-5 Likert-type scale ranging from “Strongly Disagree” to “Strongly Agree” with an open-ended “comments” item at the end of the survey for respondents to enter any comments and/or suggestions for future boot camps.

The de-identified pre- and post-boot camp survey data from both OB/GYN cohorts were entered by the analyst author (WDC) into an S.P.S.S. version 22 data set for comparative descriptive analyses.

**RESULTS**

Complete pre- and post-boot camp OB/GYN practice skills confidence and knowledge ratings data were obtained from a total of 45 resident respondents, 33 from the 2014 boot camp and an additional 12 respondents from the 2015 boot camp. Quantitative survey item data required only a minor amount of cleaning. A total of 28 open-ended qualitative comments or suggestions written in by residents were also entered into word processing software.

**Mean Pre-Post Boot Camp Practice Skills Confidence and Knowledge Differences**

Each of the total 45 resident respondents demonstrated an overall improvement in pre- to post-boot camp practice skills confidence and knowledge levels. Mean per resident pre-post boot camp responses for the shorter 2015 boot camp increased by 1.096 (SD = 0.5487) on the 1 through 5 scale, indicating that most members of the 2015 resident cohort respondents rated themselves on average as “more confident” in the specific OB/GYN skill and knowledge areas for most items than 2014 residents demonstrating a mean 0.0453 (SD = 0.1628) survey item increase. When comparing the two cohorts, mean “between group” differences were not found to be statistically significant (i.e., overall equivalent) (p = 0.241).
Figure 1 depicts the overall equivalent distributional patterns of practice skill confidence and knowledge improvements measured from the two learner cohorts. The larger number of red-colored 2014 respondents exhibit a similar distributional pattern of score improvements when compared to the smaller number of light blue-colored 2015 residents. Since they were using a newly created survey instrument, the authors avoided trying to calculate any type of composite survey score until the survey had undergone some additional refinement and possible psychometric testing in future studies.

**Individual Practice Skills Confidence and Knowledge Item Improvements**

As might be expected, the average individual resident practice skills confidence and knowledge item score increased for every item in pre and post-boot camp surveys for both cohorts. However, the following six items were those that increased the most when comparing the 2014 to 2015 boot camps:

1. “*I can discuss the fire risk score and what it means to us and our patients;*”
   (mean increase from 2.430 (in 2014) to 2.600 (in 2015))

2. “*I am able to competently repair simulated lacerations of the perineum and simulated episiotomies;*”
   (mean increase from 1.980 to 2.370)

3. “*I understand the Duty Hour Rules, how to log them, and their significance;*”
   (mean increase from 2.200 to 2.400)

4. “*I can describe and perform the closure of first degree midline episiotomy;*”
   (mean increase from 1.890 to 2.160)

5. “*I can describe the important components of “handoffs” and their importance;*”
   (mean increase from 1.850 to 2.030)

6. “*I am aware of the Statewide Campus System Research Modules.***
   (mean increase from 2.170 to 2.440)
Qualitative Resident Comments
A total of 28 (62.2% of complete data sample) respondents offered specific comments regarding what components of their respective boot camp they most appreciated or could be improved.

2014 Five-Day Boot Camp

Strengths
• Great hands on learning opportunities.
• Suturing practice every day was helpful.
• Made me less apprehensive going into intern year.
• Fetal monitoring course was awesome.
• Great review of instruments.
• Laid back lectures helped information get across.

Areas to improve
• Need more instruction on fetal heart rate monitoring steps.
• A few very repetitive lectures (Labor & Delivery).
• NEED to go over suturing in a lecture before going into hands on.
• Could be condensed to 3-4 days without all of the repetitive lectures.
• More time for Neonatal Resusciation Program (NRP).

2015 Three-Day Boot Camp

Strengths
• I did enjoy the lecture that preceded today’s lab verses yesterday because it had pictures to help us visualize.
• Excellent amount of information. I really feel it was an immense help and a great way to begin breaking into residency.
• Triage cases were the most helpful today.
• The clinical based lectures and hands on experiences we did have were very beneficial.
Areas to Improve

- I would have liked to have heard the lecture about suture types and uses of each. I feel like I am very weak in that area. I also would have liked the amniotomy drill.
- An overview of the different types of sutures and what is commonly used in different parts of C-sections, etc. would have been very helpful.
- Vaginitis lecture was good but was primarily a review.
- I would have liked for these three days to revolve around clinical education and simulated skills labs.
- In general more hands on and less lecture.
- In regard to future boot camps - a formal ultrasound lecture with images and ideally videos would be very helpful. Also, it would have been great to have the lab for amniotomy, (intrauterine pressure catheter) (IUPC), and fetal scalp electrode (FSE).

DISCUSSION

During recent years, a wide variety of sizes, types, and duration of boot camps have evolved for different types of first-year physician residents.\textsuperscript{1,3,6,10} The boot camps to date have lasted from one day to seven weeks, with a wide variation in number of hours per day, and/or days per week. Nevertheless, most reports suggest these comprise an effective tool to improve practice skills confidence and knowledge, with positive feedback from learners.\textsuperscript{11} The authors’ intentions for these boot camps were to develop an effective tool for transition from medical school to an OB/GYN residency. This was considered particularly important given the typical time constraints between graduation and starting residency as earlier described.

The overall goal of these analyses was to determine if the authors could cover the same basic content in three days and achieve equivalent learner practice skills confidence outcomes. In future boot camps, we intend to utilize additional assessment tools (pre- and post-boot camp), such as the Association of Professors of Gynecology and Obstetrics (APGO) Preparation for Ob-Gyn Residency Knowledge Assessment Tool
(PrepForRes) exam,\textsuperscript{16} to more rigorously measure effectiveness of learning and retention.

**Study Limitations**

These results should be reviewed within the context of several major limitations. Obviously, two small convenience samples of OB/GYN residents from Michigan residency programs may certainly limit the generalizability of these findings to other parts of the country. In addition, the considerably smaller size of the 2015 respondent cohort limited our ability to use inferential statistical procedures to compare learner practice skills confidence and knowledge differences between the two boot camp cohorts.

This was also the first two times that the authors had used this untested 25-item survey instrument. The manner in which the 2014 and 2015 boot camps may have differed in other unmeasured ways could also have skewed our measured cohort differences. It would also have been ideal to follow these participating OB/GYN residents longitudinally to more systematically evaluate the actual total impact of the boot camp through the perspectives of the residents and/or their residency program faculty.

**CONCLUSIONS**

There appears to be a growing consensus that there is benefit to providing a boot camp format for transition from medical school to residency.\textsuperscript{5,6,11} In addition, the Level 1 ACGME Milestones now provide a more focused set of expectations of what an incoming first-year OB/GYN resident should know or be able to perform.\textsuperscript{17} As various boot camp formats evolve, it will be important to measure the perceived value of these events by varied GME learners in addition to measuring pre- and post-training practice skill confidence levels.

Based on these initial results, the authors have determined that it may be possible to adjust the boot camp described here from five days to three and still achieve comparable practice skill confidence and knowledge outcomes while delivering the same basic OB/GYN content. While there has been a perceived benefit of providing a longer, more extensive boot camp, GME educators’ ability to provide longer multi-day events may be increasingly limited particularly by resource constraints.\textsuperscript{11,12}
Additional studies with larger resident samples of OB/GYN residents and faculty are needed to examine the most cost-effective formats and lengths of boot camps currently offered to first-year residents across the nation. Ideally, the results of these small pilot analyses can help inform the future development and testing of boot camp events to facilitate new OB/GYN residents practice preparation.

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Figure 1
Comparison of 2014 to 2015 Pre-Post Boot Camp Practice Skills Confidence and Knowledge Item Improvements

2014 or 2015 Cohort
- 2014-FIVE Day Format (n = 33)
- 2015-THREE Day Format (n = 12)

PRE-to-POST-Workshop Self-Assessment Score Improvement Category
Appendix 1

OB/GYN Boot Camp Resident Practice Skills Confidence/Knowledge Items *

1. I am aware of the Statewide Campus System Research modules
2. I am well versed on the expectations of social media as it pertains to professionalism in medicine.
3. I can discuss the components involved in the conduction of normal labor and delivery.
4. I am well versed in the instrumentation utilized in vaginal deliveries.
5. I am well versed in the names and function of the instruments used in a cesarean birth.
6. I am able to identify the different types of suture materials.
7. I can discuss the different uses of the different types of suture materials.
8. I can perform well-done one- and two-handed square knot ties.
9. I am able to competently repair simulated lacerations of the perineum and simulated episiotomies.
10. I am able to competently perform interrupted, figure of eight, running and running interlocking wound closures.
11. I am able to describe the steps in preparation for surgery and appropriate hand washing, gloving and gowning techniques.
12. I can describe three aspects of an institution that utilizes high reliability standards and its beneficial effects on patients and staff.
13. I can discuss the fire risk score and what it means to us and our patients.
14. I can describe the components of “OR Time out” and how this affects patient’s safety.
15. I can discuss the importance and components of e-Logs.
16. I understand the Duty Hour Rules, how to log them, and their significance.
17. I can describe the important components of “handoffs” and their importance.
18. I can describe the physiology of EFM and the current nomenclature to describe Electronic Fetal Monitoring tracings.
19. I can describe the pathophysiology of abnormal Electronic Fetal Monitoring tracings and the appropriate physician response to those abnormalities.
20. I can describe and perform the closure of 1st degree midline episiotomy.
21. I can describe and perform the sequence of events for fetal scalp electrode placement, intrauterine pressure catheter placement, and amniotomy.
22. I can describe the appropriate components of cervical exam and appropriate documentation.
23. I can discuss how to document rupture of membranes.
24. I can discuss proper microscope usage and how to diagnose and treat common vaginitis encountered in OB/GYN.
25. I can describe the techniques involved in evaluation of the obstetrical patient that presents to triage for evaluation.

* 1 to 5 Likert-type scale ranging from 1 = “Strongly Disagree” to 5 = “Strongly Agree”
Original Contribution

Sub-Dissociative Ketamine Use in the Emergency Department for Treatment of Suspected Acute Nephrolithiasis: The SKANS Study

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ABSTRACT

GRILL J, BRYANT C, DUNIKOSKI I, CARRASCO Z, WISNIEWSKI SJ, PRICE K. Sub-Dissociative Ketamine Use in the Emergency Department for Treatment of Suspected Acute Nephrolithiasis: The SKANS Study. Spartan Med. Res. J. Vol. 3, No. 3, 2019. CONTEXT: Currently, there is no standard therapy for treatment of acute renal colic. With the increased scrutiny and controversy now surrounding opioids, the authors identified a need to investigate an alternative medication for pain control. As such, they sought to determine the efficacy of sub-dissociative (i.e., low) doses (0.3 mg/kg) of ketamine in providing Emergency Department (ED) patients acute pain management for renal colic secondary to nephrolithiasis. METHODS: After institutional review board (IRB) approval, the authors conducted a non-blinded, prospective clinical study. A convenience sample of n = 34 patients from the ED of a Western Michigan-based health system with suspected renal colic received one intravenous dose of ketorolac, 30 mg if over 50 kg body weight or 15 mg if under 50 kg. In patients weighing greater than 50 kg, up to two doses of sub-dissociative ketamine were then given to further control pain. Pain was assessed at times 0, 30, 60, 90 and 120 minutes. RESULTS There was a statistically significant pain reduction with administration of sub-dissociative ketamine, with 24 (69.2%) patients reporting an average reduction in pain score > 30% (t = 3.16, p = 0.004). Initial average pain scores for patients receiving sub-dissociative ketamine averaged 7.76 (SD = 2.55) on the 11-point verbal Pain Numeric Rating Scale. After a first dose of ketamine, patients’ average pain score was 3.56 (SD = 0.74) at 30 minutes. After two hours, patients’ average score was 2.56 (SD = 0.65), indicating that pain control was still effective over time with no statistically significant change in pain scores. Additionally, there was no statistically significant difference in pain reduction observed between genders (t = -0.192, p = 0.850). CONCLUSIONS Based on these results, sub-dissociative ketamine may be considered a reasonable and effective supplemental non-opioid treatment option for suspected renal colic in otherwise healthy 18-70-year-old patients and could provide an effective alternative to traditional therapies. Further studies utilizing this methodology with larger, more generalizable samples are needed to further validate these findings. Keywords: sub-dissociative ketamine, renal colic, ketorolac/toradol, opioid alternative.
INTRODUCTION

Renal colic is an acute, severe, intermittent pain caused by a stone obstructing flow of urine in the genitourinary tract. Lodging of a stone within a ureter increases the hydrostatic pressure causing the urothelium to stretch and activate afferent autonomic pain fibers. These fibers originate from the Thoracic 10 through Lumbar 1 vertebrae levels resulting in known viscerosomatic reflex referred pain patterns to the flank, abdomen, groin, and/or genitalia. In the United States, acute onset renal colic represents 8.8% of all cases in the emergency departments (ED); with an estimated 1.2 million annual cases of nephrolithiasis. The lifetime risk of developing kidney stones for men in the US is 12% and 7% for women.

Treatment opinions vary between providers, sources, and facilities. Steinberg et al. found that only 69% of renal colic patients received adequate analgesia while in the ED. Increasing incidence of renal colic has been associated with increased costs; in 2009, ED services associated with treatment of renal colic were over $5 billion. Further complicating matters, a specific standard for acute renal colic pain management in ED settings does not exist.

Most evidence suggests non-steroidal anti-inflammatories are superior for analgesia with fewer side effects compared to opioids. Research has suggested concomitant opioid use with non-steroidal anti-inflammatory drugs (NSAIDs) was superior to either therapy alone; opioid usage was reduced by 49% when given with NSAIDs. Studies comparing acetaminophen with opioids and NSAIDs have yielded inconclusive results. Other alternatives such as acupuncture, antispasmodics, and fluid resuscitation have not been found to be superior than NSAIDs or opioids for analgesia. In light of the current opioid epidemic, there is also a compelling need for novel, non-narcotic pain medication for patients presenting to the ED with pain complaints. Sub-dissociative ketamine (SDK) may be a non-opioid alternative for acute pain management in emergent renal colic.

During the past decade, SDK adjusted by patient weight (<1.0 mg/kg) has been recognized as an effective treatment option for acute pain for a variety of situations such as: wound dressing for burns, perioperative pain, cancer, chronic regional pain syndrome, abscess incision and drainage, limb fractures, closed reductions, and
trauma.\textsuperscript{19-32} SDK at 0.3 mg/kg has been shown to provide effective pain control.\textsuperscript{28,29,33} To our knowledge, there have been no studies regarding the use of SDK (0.3 mg/kg) intravenous (IV) without the use of opiates for acute renal colic secondary to nephrolithiasis.

**Purpose of Study**

The purpose of this clinical, prospective study was to determine the efficacy of utilizing SDK 0.3 mg/kg IV as an analgesic agent for renal colic in a convenience sample of ED patients. The authors' hypothesis for this trial was that use of SDK would provide an effective supplemental non-opioid option for the treatment of acute renal colic in the ED with minimal adverse side effects.

**METHODS**

**Study Design and Setting**

This community-based study was a non-blinded prospective study testing the efficacy of an IV SDK dose of 0.3 mg/kg for the management of acute renal colic associated with nephrolithiasis in two EDs at a West-Michigan based health system. Before the study, the authors' institutional review board approved the study protocol. Patients were enrolled upon written agreement using an approved informed consent according to institutional policy. This study was conducted in the Mercy Health ED campuses at the Hackley and Mercy facilities in Muskegon, Michigan. Combined, these campuses provide care to greater than 100,000 patients annually. The study population included a variety of ethnicities and ages. Enrollment period began in July 2016 and ended in February 2018.

**Selection of Participants**

A convenience sample of eligible patients was obtained by board-certified emergency physicians, physician assistants, and emergency medicine residents using a standard renal colic protocol at the two ED study sites. Patients were offered participation based on clinical suspicion of nephrolithiasis after presenting with signs and symptoms of renal colic such as (but not limited to) flank, abdominal, groin or genital pain with nausea, vomiting, hematuria, and/or dysuria.

Inclusion criteria were: patients of all genders, race, and ethnicities between the
ages 18-70. Exclusion criteria included: history of ketamine abuse, pregnancy, prior admission for kidney stones in the past 90 days, contraindications to study medications, severe respiratory disorders, schizophrenia, renal impairment, peptic ulcer disease, and recent gastrointestinal or intracranial hemorrhage. Patients who satisfied all study criteria were counseled utilizing an IRB approved informed consent document.

**Interventions**

After consent was obtained, patients weighing greater than 50 kg received IV ketorolac 30 mg for analgesia (IV ketorolac 15 mg was administered if patients weighed less than 50 kg). At 30 minutes, pain was assessed using the 11-point verbal pain Numeric Rating Scale (NRS). If their pain was 5 or greater, IV ketamine 0.3 mg/kg was diluted in 50 mL of normal saline (NS) and infused over 10 minutes. This was defined as time zero. Study investigators then recorded pain scores using the 11-point verbal pain NRS as well as vital signs at 0, 30, 60, 90 and 120 minutes.

If patients were still experiencing pain after 30 minutes of the initial SDK dose, a second IV SDK dose was offered. After 90 minutes, if patients were still experiencing pain at an NRS score of 5 or greater, or requested additional medications, pain management was then implemented at the discretion of the ED provider. IV Midazolam 0.1 mg/kg was also available for patients who experienced anxiety or agitation. The data collection for each sample patient ended at time of their discharge from the ED. There were no follow up evaluations required. Discharge medications were left to the discretion of the treating provider.

**Measurements**

Data were recorded using a paper data sheet with a patient identifying sticker. These data sheets were kept in the patients’ charts until all data collection was complete. Providers were asked to record vital signs, time, dosage, verbal pain NRS and any side effects experienced by patients. The data was de-identified by our lead investigator author (JG) when all data were collected and recorded. The de-identified data sheets were then placed in locked and collection boxes kept in the ED. These boxes were periodically emptied by study team members and manually uploaded into the Research Electronic Data Capture (REDCap) software for storage and future statistical analyses. Pursuant to our study design, patients were given the option to
disenroll from the project at any time.

**Outcomes**

The primary outcome measured was pain management after IV ketamine 0.3 mg/kg. Pain was assessed using an 11-point verbal pain NRS on a 0 to 10 scale. Pain scores and vital signs were measured at times 0, 30, 60, 90 and 120 minutes. Secondary outcomes measured included any adverse side effects.

**Analyses**

Initial descriptive analyses were performed examining overall mean pain NRS scores for each intervention group, as well as among gender subgroups. Descriptive statistics were also generated for the number of recorded adverse events. Further analyses were carried out utilizing independent t tests and paired t tests to compare between intervention groups, and among initial relief of pain for ketamine with two-hour follow-up pain levels, respectively. All statistical analyses were carried out using the IBM Statistical Package for the Social Sciences (SPSS) version 25 by the fifth author (SJW), with alpha cut-offs of 0.05 and a power of 0.80 specified.

**RESULTS**

A total of n = 34 patients were enrolled in the study. Eight (23.5%) of these patients were given IV ketorolac with adequate pain relief and thus not requiring ketamine. A sample subgroup 26 (76.5%) patients were administered IV ketamine. There were n = 14 (41.2%) male subjects in the study, and n = 20 (58.8%) female subjects. Previous studies have established a 30% reduction in pain can be considered a clinically significant threshold for demarcating pain improvement.37

Our primary endpoint was therefore to determine whether SDK met or exceeded this pain reduction goal. Overall, n = 23/34 (67.6%) of sample patients reported to have a clinically significant reduction in their pain score (> 30%). Of the patients who received SDK, n = 18/26 (69.2%) of study participants had a reduction in pain score > 30%. After receiving ketamine, pain was reduced from an initial mean pain score of 7.62/10 at time 0, to a pain score of 2.44 (SD = 0.78) at 30 minutes.

Patients who did not reach the authors’ observed 30% or higher pain reduction threshold had a mean pain score after 30 minutes of 6.88 (SD = 1.17). Independent t
testing determined that these findings were significant, with a $t = 3.16$ and a $p$ value = 0.004. In addition, the effect size for this difference was large, at 1.16 (95% CI 0.36 – 1.94). This suggests that not only did a large proportion of the patients receive benefits from IV ketamine in pain relief ($n = 23/34$ (69.2%), but also that the magnitude of pain relief conferred by receiving ketamine was substantial for this group.

We were unable to identify any statistically significant difference in reduction of pain NRS scores between genders. The average initial pain NRS score reported by patients who received IV SDK was 8.14 (SD = 0.63) for men and 7.50 (SD = 0.61) for women. The 30-minute pain scores in these groups were 2.63 (SD = 1.35) for men and 4.33 (SD = 0.91) for women. Independent $t$ test analyses further revealed that this difference in 30-minute pain scores between the genders was not significant, with $t = -1.047$ and $p = 0.306$. This pain reduction was more pronounced two hours after receiving IV ketamine with mean pain for male participants of 2.38 (SD = 1.56) and a mean pain for female participants of 2.65 (SD = 0.65). Similarly, paired $t$ test analyses revealed the difference in pain NRS scores two hours after the initial dose of IV ketamine was not significant across genders, $t = -0.192$, $p = 0.850$.

The most common adverse event experienced by sample patients was dizziness (17.5%), followed by feeling “high” (10.0%), and “drunk” (5.0%). Similar symptoms were found in previous studies examining IV SDK with reports of dizziness, nausea, and emesis. All reported symptoms resolved prior to discharge without use of midazolam. Several patients received anti-emetics for their nausea although data on the type and amount of medication were not collected. No patients experienced emergent reactions from SDK doses so there were no major adverse events in our study cohort.

Although our study was not adequately powered to examine the efficacy of IV ketorolac in pain reduction for renal colic, we did note a 30% or greater pain reduction with ketorolac alone in three of eight (38%) of patients. Initial average pain NRS scores in this group were 9.2 out of 10 which decreased to 6 out of 10 after receiving ketorolac. These findings were not, however, statistically significant ($t = 1.78$, $p = 0.212$). It is interesting to note that similar pain reduction has been documented in prior studies examining IV ketorolac for treatment of pain associated with renal colic.
DISCUSSION

Our results demonstrate that SDK can be a viable therapeutic alternative to traditional treatment of renal colic in an ED setting. Several investigators have demonstrated the efficacy of low dose ketamine for a variety of patients presenting with pain complaints in the ED.19,20,24,29,30,40 During this study, we evaluated 34 patients who presented with signs and symptoms suggestive of renal colic and who received IV ketorolac followed by IV ketamine and found a statistically significant reduction in the verbal pain NRS scores that were independent of gender both initially and two hours after administration. Based on this finding, SDK can be considered an effective therapy option for the treatment of suspected renal colic in the ED.

Ketamine is a non-competitive antagonist at N-methyl-d-aspartic acid (NMDA) receptors with additional activity at mu opioid receptors. NMDA receptors are ligand-gated channels in the brain and spinal cord that bind the excitatory neurotransmitter glutamate. Current research suggests NMDA receptors are involved in pain transmission and modulation.40 The continuous binding of glutamate promotes the development of a hyperalgesia reflex arc, promoting pain via nociceptive neurons. Ketamine is thought to block this hyperalgesic pathway by antagonizing NMDA receptors, possibly explaining its unique analgesic properties.28,29,41-43 It can be administered IV, intramuscularly, intranasally, intraosseously, and by mouth. Ketamine has been shown to potentiate opioids when used simultaneously and decrease the amount required for analgesia.42-45 Ketamine-induced analgesia preserves respiratory reflexes, maintains cardiovascular stability and is not associated with hyperalgesia unlike increasing doses of opioids, making it a viable option for use in the ED for acute pain relief.44,45

Ketamine has fewer side effects (e.g., cardiopulmonary depression) than current analgesic medications used to treat renal colic. Most ED physicians avoid use of ketamine for fear of side effects, most notably emergence phenomenon featuring post-sedation hallucinations and agitation. Studies have found these events are dose-dependent and are unlikely to occur at sub-dissociative ketamine doses less than 1.0 mg/kg.37 The most common side effect of ketamine is dizziness.27,29,32,44,46 This was replicated in our study, with 17.5% of patients reporting this symptom.
The use of NSAIDs has been limited in patients with renal insufficiency, pregnancy, and history of gastrointestinal bleed, hence the reason alternatives are necessary for patients with renal colic. In contrast, with increasing doses, opioids can also cause life threatening respiratory depression and delirium.\textsuperscript{28,43} IV Ketamine has not been shown to display either of these adverse effects.

**Limitations**

Our sample size, though adequately powered for statistical analysis, was small. This makes us wary of a Type II Error that might otherwise be disproven in a larger sample size. Our results also displayed large standard deviations for a portion of mean pain NRS scores, which might have been further narrowed (i.e., more accurate) in a larger sample. Likewise, our results were generated from a relatively small geographic area with a relatively homogenous patient population. Our enrollment criteria encompassed a wide range of ages (i.e., 18-70 years).

With a larger data set, further subgroup analyses stratified by age and gender might yield additional information to determine the ideal patient groups most appropriate for use of this medication. The prior administration of IV ketorolac may have contributed to decreases in pain after the patient had received ketamine as ketorolac has a duration of action of four to six hours. Future study groups may wish to investigate the utility of ketorolac and ketamine as monotherapy during inferiority / superiority studies as compared to opioid medications.

**CONCLUSIONS**

In summary, our results indicate that IV SDK can be effective at treating pain associated with renal colic at 30 minutes and up to 120 minutes. Larger multicenter prospective studies are needed to confirm our results and ensure that they are generalizable to other ED settings and patient groups. We hope that these study results provide the basis for an expanded analgesic option in the acute management of renal colic. It behooves emergency physicians to consider non-opioid analgesia options in the midst of the current opioid epidemic and there is growing literature to support the use of SDK for acute pain management.
The authors report no external funding source for this study

The authors declare no conflict of interest

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REFERENCES


### Table 1
**Sample Patient Demographics**

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<th>Age (mean) (SD)</th>
<th>Gender</th>
<th>Weight (kg) (SD)</th>
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<tr>
<td><strong>Total</strong></td>
<td>40.65 (14.87)</td>
<td>F 55.6% M 38.9%</td>
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<td><strong>Ketamine</strong></td>
<td>41.69 (15.10)</td>
<td>F 69.2% M 30.8%</td>
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<tr>
<td><strong>Ketorolac</strong></td>
<td>37.25 (14.54)</td>
<td>F 25.0% M 75.0%</td>
<td>96.6 (25.79)</td>
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<td>(n = 8)</td>
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</table>

### Table 2
**Mean Pain NRS Scores after Ketamine and Ketorolac**

<table>
<thead>
<tr>
<th></th>
<th>Original pain score (SD)</th>
<th>Pain score after ketamine (SD)</th>
<th>Pain score after ketorolac (SD)</th>
<th>Pain reduction 30% (n =)</th>
<th>Pain after 2 hrs (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>7.76 (.437)</td>
<td>-</td>
<td>-</td>
<td>n = 23 (67.6%)</td>
<td>-</td>
</tr>
<tr>
<td>(n = 34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ketamine</strong></td>
<td>7.76 (.437)</td>
<td>3.53 (.661)</td>
<td>-</td>
<td>n = 18 (69.2%)</td>
<td>2.56 (3.24)</td>
</tr>
<tr>
<td>(n = 26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ketorolac</strong></td>
<td>7.76 (.437)</td>
<td>-</td>
<td>2.63 (.399)</td>
<td>n = 5 (62.5%)</td>
<td>-</td>
</tr>
<tr>
<td>(n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3
**Doses of Ketamine, Number of Adverse Events, and Additional Pain Medication, Relief with Ketorolac Alone**

<table>
<thead>
<tr>
<th></th>
<th># of doses of ketamine</th>
<th>Adverse events</th>
<th>Additional medication</th>
<th>Relieved with ketorolac alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (n = 34)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dose (52.8%)</td>
<td>n = 14 (38.9%)</td>
<td>n = 7 (19.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 doses (19.4%)</td>
<td>2 doses (19.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ketamine (n = 26)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>n = 6 (23.1%)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ketorolac (n = 8)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>n = 8 (100%)</td>
<td>-</td>
<td></td>
<td>8/32 = 25%</td>
</tr>
</tbody>
</table>

### Table 4
**Differences in Mean Pain NRS Scores across Gender and Pain Reduction Threshold (30%)**

<table>
<thead>
<tr>
<th></th>
<th>Male (mean pain)</th>
<th>Female (mean pain)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>After Ketamine</strong>*</td>
<td>2.63 (SD = 1.35)</td>
<td>4.33 (SD = 0.91)</td>
<td>p = 0.31</td>
</tr>
<tr>
<td><strong>2 Hours after Ketamine</strong></td>
<td>2.38 (SD = 1.56)</td>
<td>2.65 (SD = 0.65)</td>
<td>p = 0.85</td>
</tr>
<tr>
<td><strong>After ketorolac</strong>*</td>
<td>3.33 (SD = 1.82)</td>
<td>0.50 (SD = 0.50)</td>
<td>p = 0.19</td>
</tr>
<tr>
<td><strong>Pain Reduction</strong></td>
<td>&lt; 30%, 6.88 (SD = 1.17)</td>
<td>&gt; 30%, 2.44 (SD = 0.78)</td>
<td>p = 0.004</td>
</tr>
<tr>
<td><strong>Effect size</strong></td>
<td>4.47 (95 % CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Independent T-test performed  
** Paired T-test performed  
*** Pain reduction < of > 30% for the ketamine group (no gender differences examined)  

NRS  Numerical Rating Scale
Ensuring Patient Safety in Emergency Peripheral Ultrasound-Guided Nerve Blocks: An Evaluation of a Quality Improvement/Patient Safety Initiative

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ABSTRACT

WAHL DJ, BUTKI AJ, BUTKI N, WISNIEWSKI SJ. Ensuring Patient Safety in Emergency Peripheral Ultrasound-Guided Nerve Blocks: An Evaluation of a Quality Improvement/Patient Safety Initiative. Spartan Med. Res. J. Vol. 3, No. 3, 2019. CONTEXT: During the past two decades, bedside ultrasound has revolutionized the practice of emergency medicine, with physicians now expected to be competent in utilizing ultrasound skills for patients presenting with conditions ranging from trauma to skin evaluations. The overall purpose of this quality improvement/patient safety (QIPS) project was to evaluate the effectiveness of a pair of five-hour, hands-on didactic/training sessions, aimed at preparing a sample of emergency medicine physicians, residents and medical students to perform peripheral ultrasound-guided nerve blocks. METHODS: The study location was set in a community-based emergency medicine program in Pontiac, Michigan. Data was collected from N = 54 emergency medicine residents, physicians and medical students. Data were collected from two training sessions in November 2017 and January 2018. The training consisted of a 12-question pre-test, followed by five hours of hands on & didactic training, with a subsequent post-test containing the same questions. RESULTS: The authors compiled the data from both training sessions and found that the participants had an average correct percentage of 5.52 of 12 (46%) on the pre-test. After attending the training session, participants had an overall correct percentage of 9.24 of 12 (77%) on the post-test. This pre-to post-training increase of the mean scores was statistically significant, t (53) = -10.76 (p < 0.01), with an effect size (Cohen’s d) of 1.82. Post hoc power calculations utilizing the d = 1.82 effect size revealed statistical power (1 - β) of 100%. CONCLUSIONS: The results of this QIPS evaluation project suggest that emergency physicians, residents and medical students may achieve an improved understanding of key ultrasound-guided nerve block material after a single five-hour session of hands-on training and didactics. Going forward, additional studies employing larger sample sizes that allow for outcome stratification by group (emergency physicians, residents, or medical students) along with relevant demographic variables (age, years in practice, etc.) in similar settings are needed to further verify these findings. Keywords: ultrasound, peripheral nerve-block procedures, emergency medicine, patient safety
INTRODUCTION

During the past two decades, bedside ultrasound has revolutionized the practice of emergency medicine (EM). The next generation of emergency physicians are expected to be competent in utilizing ultrasound (US) skills for patients presenting with conditions ranging from trauma to skin evaluations. A rapidly evolving use of bedside ultrasound in EM is combining fine motor skills with knowledge of peripheral nervous system anatomy and physiology to perform US-guided nerve blocks.

The history of US-guided regional anesthesia has quickly evolved over the last 25 years. In 1989, Ting and Sivagnanaratnam described using ultrasonography to localize a needle while performing an axillary nerve block. They reported no patient complications, due to visualizing the needle and surrounding anatomy at all times. In 1994, Kapral et al. demonstrated the benefits of US for supraclavicular blocks. Subsequent studies have demonstrated that the use of US guidance allowed for smaller amounts of local anesthetic to produce an effective nerve block.

As US technology has improved access to the bedside in emergency department (ED) settings, a team of Toronto physicians in 2003 were able to demonstrate adequate localization of patients’ brachial plexuses with high-quality images. Since then, the use of bedside US has revolutionized EM, particularly in regional anesthesia. In 2006, Blaivas and Lyon described four cases of shoulder dislocations, in which regional anesthesia was successful after performing US-guided interscalene brachial plexus blocks. In 2010, Chandra, et al. published a paper describing the history and patient benefits of US-guided nerve blocks in the ED.

The benefits of performing peripheral US-guided nerve blocks in ED settings are numerous. They range from joint dislocation reduction, wound care, fracture reduction, decreased use of procedural sedation and lower amounts of opioids required to reduce pain. The risk of iatrogenic injury or complications from US-guided nerve blocks has been shown to be lower than when performed blindly. However, there is still potential for unintended intravascular injections of local anesthetic, local anesthetic systemic toxicity, intraneural injections, accidental vascular punctures, hematoma formation, pneumothorax, allergy to local anesthetic, and infection. However, multiple earlier
studies have demonstrated that providers can perform US-guided nerve blocks successfully in both pediatric and adult patients in the ED setting.13-22

Project Purpose

The purpose of this quality improvement/patient safety (QI PS) project was to evaluate the effectiveness of a single five-hour, hands-on didactic/training session at preparing EM physicians, residents and medical students to perform peripheral US-guided nerve blocks. During training sessions, participants were also taught how to recognize and treat potential complications from US-guided nerve blocks. Participants' understanding of training session content was evaluated utilizing pre- and post-session test scores. The authors’ goal was to demonstrate a statistically significant improvement between pre- and post-test scores.

METHODS

IRB exemption was obtained from McLaren IRB prior to conducting the US training. Participants were EM physicians, residents and a small number of medical students. Learners were administered a knowledge quiz comprised of 12 questions for the pre-test without knowing the correct responses (Appendix A). The questions were created by the first and second authors of this paper (DJW and AJB). Data for both the pre and post-tests utilized Kahoot “Learning Games|Make Learning Awesome!” as the digital platform for trainees to submit their answers in real-time, via their personal cell phones, tablets or computers.23

The didactic and motor skills training consisted of a five-hour training session. The training began with a one-hour US didactic presentation, which covered patient safety topics associated with providing peripheral US-guided nerve blocks. Specific topics included: a) dosing for regional anesthesia, b) appropriate monitoring to ensure patient safety, c) intralipid antidote for local toxicity and d) duration of action of local anesthetics. Participants were also taught the anatomy of specific nerves and their surrounding structures. That knowledge was then applied in live-session training, as participants gained the key technical skills needed to provide US-guided nerve blocks.

The specific nerve blocks taught included the Median n., Ulnar n., Radial n., Femoral n., Popliteal n. and Tibial n. These nerve blocks were taught by the first two
authors (DJW and AJB), who are trained in US-guided nerve blocks (New York School of Regional Anesthesia and Emergency Ultrasound Fellowship, respectively). The nerve blocks that were taught during this course were selected based on level of difficulty, usefulness in routine EM care and relative safety profile.

Learners' motor skills were developed during breakout sessions, during which participants identified the six previously listed nerves using US on participant colleagues. Participants also used a Blue Phantom™ nerve block task trainer to acquire the motor skills of needle-nerve localization and anesthetic injection.

Following this didactic and motor skills training, participants were asked to take the same 12-item test as a post-test. Training sessions were performed on two separate days to maximize participants. The trainings took place in November 2017 and January 2018, with a total of 54 participants. The same trainers (DJW and AJB) taught both sessions, for consistency of material delivery. Results were not analyzed until after the second training session. The results of participants were only analyzed for those individuals who had completed both the pre and post-tests and attended the entirety of the didactic and motor skills training sessions.

**Statistical Analysis**

Pre- and post-test scores were first compared on a base descriptive level for each day of training (e.g., one in November 2017, and one in January 2018). Post hoc two-tailed power calculations assuming a moderate effect size (0.5) and an alpha of 0.05 were also performed. After verifying distributional assumptions, a series of Wilcoxon Matched Paired t-Tests were also performed comparing pre- and post- mean test scores for all participants over the two days of training. All statistical analyses were performed by the fourth author (SJW) utilizing SPSS Version 25 analytic software.

**RESULTS**

Thirty-six participants were enrolled the first training day in November 2017. The participants scored an average overall correct response of 4.89 out of 12 (41%) on the pre-test. Subsequently, the participants scored an average overall correct response of 8.78 out of 12 (73%) on the post-test. Eighteen participants were enrolled on the second training day, in January 2018. The participants scored an average overall correct
response of 6.78 out of 12 (57%) on the pre-test. The participants subsequently scored an average overall correct response of 10.17 out of 12 (85%) on the post-test.

The combined results of the 54 participants scored an average overall correct response of 5.52 out of 12 (46%) on the pre-test. The combined participants scored an average overall correct response of 9.24 out of 12 (77%) on the post-test. This pre-to-post increase in mean scores were statistically significant, $t(53) = -10.76 \ (p < 0.001)$, with an effect size (Cohen’s $d$) of 1.82. Post hoc power calculations utilizing the $d = 1.82$ effect size revealed statistical power ($1 - \beta$) of 100%.

DISCUSSION

Complications from peripheral nerve blocks are rare, but can be potentially catastrophic (e.g., systemic local anesthetic toxicity). As US-guided regional anesthesia continues to be increasingly utilized in the ED, the authors aimed to assess how effectively key concepts about patient safety were being taught. The group composition on the two training days of the study did not vary significantly, with similar pre- and post-test score improvements obtained from both groups.

The authors’ goal of obtaining a statistically significant overall improvement between the pre- and post-test scores was consistently realized. The combined results of participants’ correct pre-test answers was a mere 46% ($n = 54$) for the series of safety questions about local anesthetic dosage, concentration, nerve block technique, etc. (Appendix A). Following the training sessions, the combined participants scored an average overall correct response of 77% ($n = 54$) on post-tests. This suggests that our training protocol may have been effective at introducing important patient safety considerations for peripheral US-guided nerve blocks to participants.

Limitations

After analyzing our results and study design, we have identified several project limitations. First, we collected limited demographic data about the participants. We had only asked participants for information concerning their current training status (i.e., attending physician, resident physician and medical student). In future studies, demographic variables such as years in practice, number of years utilizing US technologies in EM settings and age of participants could be helpful for more detailed
sub-group analysis. Additionally, the size of our community-based convenience sample was small. Although this project enrolled the majority of EM physicians in our Pontiac, Michigan institution, a larger sample size would be needed to perform more granular subgroup analyses. Furthermore, the pre- and post-session knowledge tests utilized during this study had not been previously validated. The questions were designed to target what the first two authors concluded to be the most important safety aspects of performing US-guided nerve blocks. Future training studies could include validated exams to more fully analyze learner outcomes.

CONCLUSIONS

Since ultrasound technology’s early adoption in the late 1980s, more powerful bedside machines are now readily available. This has allowed US-guided nerve blocks to become more common in today’s emergency medicine practice. As ultrasound technology has improved, so have the skills of those performing bedside US procedures. As a profession, we need to ensure that patient safety knowledge escalates at a similar rate of skill acquisition. These project results demonstrate the potential for success in teaching patient safety to EM physicians, residents and medical students to perform US-guided nerve blocks. In the future, similarly structured training protocols could be implemented when teaching emergency physicians to perform these valuable patient treatment skills with a bedside ultrasound.

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The authors declare no conflict of interest.

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TABLES AND FIGURES

Appendix A
Ultrasound Nerve Block Pre and Post-Test Questions with Answers
(correct answers in bold)

1. What is the maximum amount of lidocaine without epinephrine that can be safely administered into the soft tissue?

   3.5 mg/kg
   7 mg/kg
   **4.5 mg/kg**
   8 mg/kg

2. What is the maximum amount of lidocaine with epinephrine that can be safely administered into the soft tissue?

   4 mg/kg
   **7 mg/kg**
   5 mg/kg
   8 mg/kg

3. What is the concentration per mL of 1% lidocaine without epi?

   12 mg/ml
   15 mg/ml
   20 mg/ml
   **10 mg/ml**

4. What medication needs to be administered quickly via IV in the event of a toxic reaction to local anesthesia?

   Glucagon
   D50
   **Intralipid**
   Pyridoxine
5. For the majority of ultrasound guided nerve blocks, what needle approach is recommended to maximize safety?

- Seldinger technique
- **In-plane technique**
- Out-of-plane technique
- Oblique technique

6. Of the medications listed below, which one is the most cardio-toxic?

- Bupivacaine
- Lidocaine without epi
- Ropivacaine
- Lidocaine with epi

7. What is the earliest sign that lidocaine with epinephrine has entered the bloodstream?

- Increased salivary secretions
- **Increased heart rate**
- Increased respirations
- Decreased hearing

8. A patient has a large laceration. Local infiltration of 1% lidocaine without epinephrine lasts roughly 45 minutes. How long (anesthesia time) does a typical block using the same lidocaine without epinephrine last?

- 45-60 min
- **90-180 min**
- 180-260 min
- 30-60 min

9. What are the EKG findings in local anesthesia toxicity?

- Narrow QRS, Bradycardia, Hypertension
- Narrow QRS, Tachycardia, Hypertension
- Wide QRS, Tachycardia, Hypotension
- **Wide QRS, Bradycardia, Hypotension**
10. When using 0.5% Ropivacaine for a block, what is the expected onset time for the block to begin working?

- 15-30 min
- 10-15 min
- 5-10 min
- Less than 5 min

11. What is recommended dose of Lipid Emulsion for a 70 kg lean body weight adult?

- 70 mL
- 100 mL
- 120 mL
- 150 mL

12. Once the needle is through the fascial plane, if you encounter resistance while placing local anesthesia around a nerve bundle you should:

- Push through the resistance
- **Pull needle back and abandon the block**
- Pull needle back, reposition and then continue the block
- Advance needle 0.5cm farther and push 1 mL of anesthesia
Inverted Papilloma of the Middle Ear and Mastoid Cavity: A Case Report, Literature Review, And Surveillance Proposal

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ABSTRACT


INTRODUCTION TO THE TOPIC: Inverted papilloma is a rare condition of the middle ear. In this paper, the authors present a case report of a patient at a Midwestern health system with inverted papilloma. To supplement the case report, a literature review was also performed to identify clinical trends predisposing such cases to recurrence, malignant transformation, and response to radiation. In addition, the authors also propose a surveillance algorithm derived from this case and previously published surveillance strategies.

CASE REPORT: The author’s present a rare case of inverted papilloma of the middle ear. To the authors' knowledge, this is the youngest case presentation (mid-teenage years) of this condition to have been reported in the literature. The patient underwent surgical excision, had recurrence, and has been disease free since revision surgery.

SUMMARY OF THE EVIDENCE: Our literature review identified 25 cases previously published with ours being the 26th. An inadequate number of cases exist to abstract statically relevant clinical trends in presentation and tumor behavior. Additionally, no tumor characteristics have been identified that predispose tumors to future malignant transformation. No assessments can be made regarding the benefits of radiation therapy. Most cases to date have been surveyed with a combination of CT, MRI, and clinical follow-up.

CONCLUSIONS: Inverted papillomas of the middle ear space are rare. Although this case report adds to the literature, additional cases are needed to draw statistically relevant clinical characteristics and responses to medical and surgical therapy. Keywords: pediatric middle ear masses, inverting papilloma, pediatric otology, pediatric skull base surgery
INTRODUCTION

Inverted papillomas are benign tumors typically found in the nasal cavity. These locally aggressive tumors have a potential for malignant transformation. Presentations of inverted papillomas in the middle ear space are rare, with the previous literature reporting as few as 23 cases total.¹ In this paper, the authors will report a case of a recurrent inverted papilloma of the middle ear space and present a comprehensive literature review of previously reported cases of this type of inverted papilloma. Finally, a surveillance algorithm-based protocol will be proposed for monitoring of recurrence.

CLINICAL CASE

A female in her mid-teens presented with a chief complaint of hearing loss. Initial otoscopic examination revealed a bulging tympanic membrane with an inflamed mass occupying the middle ear space. Nasopharyngoscopy (i.e., an endoscopic exam of the nasal cavity) did not reveal any sinonasal masses or lesions. A hearing test demonstrated a unilateral, profound hearing loss. (Figure 1)

A CT scan of the temporal bones showed nonspecific, complete opacification of the middle ear and mastoid on the affected side. (Figure 2) An additional MRI scan was obtained showing an enhanced soft tissue mass centered within the left middle ear cavity. No intracranial involvement was noted.

As seen in Figure 3, there was a proliferation of thickened transitional-type epithelium with an inverted growth pattern, forming well-circumscribed lobules and glands that emptied onto the luminal surface. No evidence of infiltrative growth or necrosis was seen. On higher power (inset) the neoplastic cells had features of columnar and stratified squamous cells lacking significant mitotic activity or nuclear pleomorphism. Intraepithelial polymorphonuclear neutrophilic granulocytes were noted, which focally form microabscesses.

The patient was brought to the operating room for a middle ear exploration and biopsy. A red, flesh-like mass was noted to be completely occupying the middle ear space. The mass appeared to be highly vascularized with finger-like projections extending radially. At the time of this exploration, the ossicular chain (i.e. the hearing bones) was...
completely encompassed in tumor and we were unable to ascertain proper anatomy and movement.

The Eustachian tube, (i.e., the narrow passage that leads from the pharynx to the cavity of the middle ear and permits the equalization of pressure on each side of the eardrum), could not be adequately viewed. A specimen of the mass was taken for pathologic review. Final pathology was interpreted as an inverted papilloma with no evidence of dysplasia (i.e. abnormal cell types suggestive of a malignant process).

After further discussion and planning by the authors, the patient underwent a surgical middle ear exploration with removal of the lesion and hopeful exteriorization. During the case, a 1 cm area of erosion of the bony eustachian tube was noted and subsequently, packed. The tumor was completely excised with the exception of two areas. A microscopic tumor was left as it was overlying facial nerve. Also, several microscopic tumor fragments were left affixed to the stapes around the oval window. Postoperatively, the patient did very well with no facial nerve weakness, although her hearing remained poor on the diseased side.

After 18 months of follow-up observation, she developed further hearing loss and ear drainage in the affected ear. A subsequent MRI demonstrated a tumor enhancement in the left mastoid region and left middle ear cavity. In addition, no enhancing lesions in either internal auditory canal were observed. No other lesions were noted in either the nasopharynx or neck.

The patient then underwent a revision modified radical mastoidectomy. Granulation tissue was noted in the mastoid cavity. There were some areas of inflammation and pockets of purulent (i.e., pus-filled) material, which were removed. Biopsies were obtained from the remnant tissue around the stapes and the facial nerve and were confirmed to be inverted papilloma. Small areas of remnant tumor along the facial nerve were left alone. She had normal postoperative facial nerve functioning. Her ear canal has since become fibrosed, scarred, and created an overclosed ear canal.

The patient has been asymptomatic since revision surgery with stable hearing loss. A pair of postoperative MRI films performed at one and six months after the second surgery showed a clear mastoid cavity with no evidence of recurrence.
SUMMARY OF THE EVIDENCE

The authors conducted a literature review to identify a total of 25 previously published cases of inverted papilloma of the middle ear and mastoid cavity, ours being the 26th. Publication dates ranged from 1987-2016. 2,3 (Table 1) Twelve (46.2%) of the 26 cases had a history of sinonasal papilloma. The average age at presentation was 51.7 years. Notably, our case presented in this paper has the youngest age at presentation (mid-teens). The other earliest published age for a patient with this condition had been in their late-teens.4,5 Variations of this condition have existed in both presentation and tumor behavior.

Hearing loss appears to be the most common presenting symptom. Interestingly, there appears to be no correlation between severity of presenting symptoms and chance of recurrence. In 2012, Jones et al. described a case that presented with complete facial nerve paralysis, although no recurrence after resection was reported.6 Conversely, several cases of hearing loss as a presenting symptom have reported multiple recurrences despite surgical and medical management.4

Additional discrepancies exist in the literature regarding whether or not radiation therapy can decrease the probability of disease recurrence. Although radiation therapy has been shown to be an effective means of local control in some instances of sinonasal inverted papillomas,7 little evidence exists with regards to its role in treatment of middle ear papillomas. However, there were also multiple cases that presented recurrence despite aggressive radiotherapy.9-11 In 2002, Pou et al. describes a case in which post-operative radiation appears to have prevented known recurrence.12

Conflicts also exist regarding whether or not a history of sinonasal papilloma predisposes patients to more aggressive malignant forms of ear papillomas. Several previous reports have described patients with a history of nasal papilloma with malignancy as the original otologic histology.5,9,12,13 Alternatively, multiple cases have been presented with patients who have a strong history of sinonasal papillomas who never demonstrated any malignant transformation of otologic tumors.6,11,14

In this presented case of a patient in her mid-teens, many factors may have been relevant to her surgical outcome. During her first tympanomastoidectomy, the decision had been made to leave the tumor over her facial nerve and around the stapes alone to
avoid facial nerve damage and deafness respectively. At the time, it was not known how aggressive the tumor was and the decision for observation was made.

During the second surgery, meticulous care was taken to remove every part of the tumor around these areas. At the time of this publication the patient is approximately 18 months out from her last surgery and disease free, although time will tell concerning the aggressive nature of her disease. Our original decision to forego radiotherapy on this patient was made due to her young age and the lack of supporting evidence in the literature. We would have chosen to radiate the area if there had been any evidence of malignant transformation, further erosion, or spread of tumor.

CONCLUSIONS

We plan to continue following the patient with serial MRIs at six-month intervals and physical exams including nasopharyngoscopy. Additional cases must be identified and published to draw statistically relevant clinical characteristics and responses to various medical and surgical therapies. Future publications that identify different presentation trends, treatment regimens, and surveillance protocols may lead to more evidenced-based patient care for this rare condition. The authors suggest that any patient with chronic ear drainage, hearing loss without obvious cause, or chronic otalgia (i.e. earache) be referred to an otolaryngologist for further evaluation.

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The authors declare no conflicts of interest.

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REFERENCES

## Table 1
Summary of Previously Discussed Cases¹-⁶, ⁸-²³

<table>
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<tr>
<th>Author</th>
<th>Presenting Symptoms</th>
<th>Age at Diagnosis</th>
<th>Sex</th>
<th>Radiation</th>
<th>History of Nasal Papilloma?</th>
<th>Histology</th>
<th>Surgery</th>
<th>Recurrance</th>
<th>Monitored With</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schaefer</td>
<td>Hearing loss, otorrhea</td>
<td>46</td>
<td>Male</td>
<td>No</td>
<td>No</td>
<td>Schneiderian type papilloma, no evidence of malignancy</td>
<td>Radiocal mastoidectomy, repair of tegmen dehiscence</td>
<td>None reported</td>
<td>Not stated</td>
</tr>
<tr>
<td>Rubin</td>
<td>Hearing loss, otorrhea</td>
<td>73</td>
<td>Male</td>
<td>No</td>
<td>No</td>
<td>Papilloma, no evidence of malignancy</td>
<td>Open tympanoplasty</td>
<td>None reported</td>
<td>MRI/CT</td>
</tr>
<tr>
<td>Nath</td>
<td>Hearing loss, otorrhea</td>
<td>60</td>
<td>Male</td>
<td>Yes</td>
<td>No</td>
<td>Inverted papilloma with marked dysplasia</td>
<td>Radical mastoidectomy</td>
<td>Yes, 11 month post treatment</td>
<td>MRI</td>
</tr>
<tr>
<td>Stone</td>
<td>Otalgia, otorrhea</td>
<td>55</td>
<td>Male</td>
<td>Yes, after recurrence</td>
<td>Yes</td>
<td>Epithelial papilloma with focal atypia</td>
<td>Modified radical mastoidectomy</td>
<td>Yes, none after radical mastoidectomy and radiation</td>
<td>CT</td>
</tr>
<tr>
<td>Kaddour</td>
<td>Otalgia, otorrhea</td>
<td>87</td>
<td>Female</td>
<td>No</td>
<td>Yes</td>
<td>Transitional cell papilloma</td>
<td>None, patient poor surgical candidate</td>
<td>Not resected</td>
<td>Clinically with occasional EAC debulking</td>
</tr>
<tr>
<td>Roberts</td>
<td>Hearing loss, otalgia</td>
<td>19</td>
<td>Female</td>
<td>No</td>
<td>No</td>
<td>Atypical inverted nests of epithelium</td>
<td>Tymanomastoidectomy with a facial recess approach</td>
<td>None</td>
<td>Serial middle ear exploration</td>
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<tr>
<td>Seshul</td>
<td>Hearing loss, unilateral serous otitis media s/p resection nasally</td>
<td>31</td>
<td>Female</td>
<td>Yes</td>
<td>Yes</td>
<td>Inverted papilloma</td>
<td>Radical mastoidectomy</td>
<td>Yes, malignant transformation, multiple recurrences in ear and nasal cavity</td>
<td>Clinically/MRI/CT</td>
</tr>
</tbody>
</table>

¹-⁶, ⁸-²³: Inverted Papilloma of the Middle Ear and Mastoid Cavity

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<table>
<thead>
<tr>
<th>Author</th>
<th>Presenting Symptoms</th>
<th>Age at Diagnosis</th>
<th>Sex</th>
<th>Radiation</th>
<th>History of Nasal Papilloma?</th>
<th>Histology</th>
<th>Surgery</th>
<th>Recurrence</th>
<th>Monitored With</th>
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<tbody>
<tr>
<td>Wenig</td>
<td>Conductive hearing loss, otalgia</td>
<td>31</td>
<td>Female</td>
<td>No</td>
<td>Unknown</td>
<td>Epidermoid papilloma with features of both inverted and cylindrical cell papilloma</td>
<td>Myringotomy with simple surgical excision; radical mastoidectomy</td>
<td>Multiple</td>
<td>CT</td>
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<td></td>
<td>Otorrhea; polypoid mass protruding from middle ear</td>
<td>56</td>
<td>Female</td>
<td>No</td>
<td>Unknown</td>
<td>Epidermoid papilloma with exophytic and endophytic growth</td>
<td>Tymanomastoidectomy, ultimately necessitating radical mastoidectomy</td>
<td>Multiple</td>
<td>CT</td>
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<td>Chronic otorrhea</td>
<td>19</td>
<td>Female</td>
<td>No</td>
<td>Unknown</td>
<td>Epidermoid papilloma with features of cylindrical cell papilloma</td>
<td>Tymanomastoidectomy</td>
<td>None</td>
<td>CT</td>
<td></td>
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<tr>
<td>Hearing loss, otalgia</td>
<td>57</td>
<td>Female</td>
<td>No</td>
<td>Unknown</td>
<td>Epidermoid papilloma with features of cylindrical cell papilloma</td>
<td>Myringotomy with simple surgical excision; treated by myringotomy and simple excision but ultimately necessitating radical mastoidectomy</td>
<td>Multiple</td>
<td>CT</td>
<td></td>
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<tr>
<td>Jones</td>
<td>Hearing loss, complete facial nerve paralysis</td>
<td>35</td>
<td>Female</td>
<td>No</td>
<td>Yes</td>
<td>Inverted papilloma, an extension of sinonasal disease</td>
<td>Fisch type C temporal bone resection</td>
<td>No</td>
<td>Clinically</td>
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<td>Chhetri</td>
<td>Aural fullness, hearing loss</td>
<td>26</td>
<td>Male</td>
<td>No</td>
<td>No</td>
<td>Epidermoid papilloma with features of cylindrical cell papilloma</td>
<td>Tymanomastoidectomy facial recess approach</td>
<td>Yes</td>
<td>Not stated</td>
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<td>Sex</td>
<td>Radiation</td>
<td>History of Nasal Papilloma?</td>
<td>Histology</td>
<td>Surgery</td>
<td>Recurrence</td>
<td>Monitored With</td>
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<td>----------------------------------------</td>
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<tr>
<td>Pou</td>
<td>Hearing loss, otorrhea</td>
<td>81</td>
<td>Male</td>
<td>Refused by patient</td>
<td>Yes</td>
<td>Carcinoma within the inverting papilloma</td>
<td>subtotal temporal bone resection</td>
<td>Yes</td>
<td>MRI + CT</td>
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<td>Hearing loss, otorrhea</td>
<td>54</td>
<td>Male</td>
<td>Yes</td>
<td>Yes</td>
<td>Inverting papilloma with squamous cell carcinoma</td>
<td>right-side subtotal temporal bone resection, sparing the otic capsule and facial nerve</td>
<td>No</td>
<td>MRI + CT</td>
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<td>de Filippis</td>
<td>Aural fullness, hearing loss</td>
<td>58</td>
<td>Male</td>
<td>No</td>
<td>No</td>
<td>Papillary neoplasia</td>
<td>Tympanomastoidectomy</td>
<td>No</td>
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<td>Mazlina</td>
<td>Otorrhea</td>
<td>54</td>
<td>Male</td>
<td>Yes</td>
<td>Yes</td>
<td>Inverted papilloma with an area of malignant transformation</td>
<td>Patient refused</td>
<td>Not stated</td>
<td>Not stated</td>
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<tr>
<td>Ali</td>
<td>Hearing loss, otorrhea, tinnitus</td>
<td>42</td>
<td>Female</td>
<td>No</td>
<td>No</td>
<td>Exophytic papillomatous neoplasm composed of non-keratinized squamous mucosa with central fibrous core consistent with Schneiderian papillomatosis</td>
<td>Tympanomastoidectomy</td>
<td>No</td>
<td>CT</td>
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<td>Acevedo-Henao</td>
<td>found on CT hx of sinonasal disease</td>
<td>63</td>
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<td>Yes</td>
<td>Yes</td>
<td>Inverted papilloma</td>
<td>Right subtotal petrectomy</td>
<td>Yes</td>
<td>MRI/CT</td>
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<td>Inoue</td>
<td>Aural fullness</td>
<td>53</td>
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<td>No</td>
<td>No</td>
<td>Squamous papilloma without cell atypia.</td>
<td>Type I tympanoplasty and complete mastoidectomy.</td>
<td>Not stated</td>
<td>Not stated</td>
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<td>Sex</td>
<td>Radiation</td>
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<td>Histology</td>
<td>Surgery</td>
<td>Recurrence</td>
<td>Monitored With</td>
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<tr>
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<td>-----------------------------------------------</td>
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<td>----------------</td>
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<tr>
<td>Zhou</td>
<td>Otorrhea, diplopia</td>
<td>52</td>
<td>Male</td>
<td>Yes</td>
<td>No</td>
<td>High grade squamous intra-epithelial neoplasia</td>
<td>Canal wall down mastoidectomy, Fisch Type A temporal bone resection. Temporalis muscle flap</td>
<td>No</td>
<td>Not stated</td>
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<td>Shen</td>
<td>Aural fullness, hearing loss</td>
<td>56</td>
<td>Male</td>
<td>Yes</td>
<td>Yes</td>
<td>Inverted papilloma</td>
<td>Radical tympanomastoidectomy</td>
<td>No</td>
<td>CT</td>
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<td>Kainuma</td>
<td>Hearing loss, otaglia</td>
<td>65</td>
<td>Male</td>
<td>Yes</td>
<td>Yes</td>
<td>Inverting Schneiderian papilloma with areas of squamous dysplasia and carcinoma in situ</td>
<td>Radical tympanomastoidectomy</td>
<td>Yes</td>
<td>Not stated</td>
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<td>Mitchell</td>
<td>Middle ear mass</td>
<td>69</td>
<td>Female</td>
<td>No</td>
<td>Yes</td>
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<td>Anterior skull base resection, temporal bone resection</td>
<td>No</td>
<td>MRI</td>
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<td>Dingle</td>
<td>Aural fullness, hearing loss (bilateral)</td>
<td>52</td>
<td>Male</td>
<td>Yes</td>
<td>Yes</td>
<td>Invasive carcinoma with evidence of Schneiderian papilloma</td>
<td>Bilateral canal wall up tympanomastoidectomy</td>
<td>No</td>
<td>MRI</td>
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Figure 1
Audiogram Obtained at Presentation. Graphs Show Unilateral, Left, Mixed Profound Hearing Loss

PTA: 8  SRT: 5

Word Recognition
Air Conduction 90% at 80 dBHL

PTA: 100  SRT: 100

Air Conduction 0% at 100 dBHL

<table>
<thead>
<tr>
<th>AIR CONDUCTION (A/C)</th>
<th>BONE CONDUCTION (B/C)</th>
<th>No Response</th>
<th>Sound Field</th>
<th>S</th>
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<tbody>
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<td>Unmasked</td>
<td>Masked</td>
<td>Unmasked</td>
<td>Masked</td>
<td>Unspecified</td>
</tr>
<tr>
<td>R</td>
<td>☐</td>
<td>☀</td>
<td>&lt;</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>☧</td>
<td>☐</td>
<td>&gt;</td>
<td>}</td>
</tr>
</tbody>
</table>

No response, air(L) at equipment limits: 8000 Hz, 250 Hz
Figure 2
Axial-cut CT Showing Left Middle Ear Mass
Figure 3
MRI of Left Middle Ear Cavity: Proliferation of Thickened Transitional-type Epithelium with an Inverted Growth Pattern, Forming Well-circumscribed Lobules and Glands that Empty Onto the Luminal Surface
**Hepatitis A:**
**A Case Report Example of a Growing Epidemiological Threat**

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1 Emergency Medicine Resident, McLaren Macomb
2 Emergency Medicine Faculty, McLaren Macomb

Corresponding Author: Adam Foster DO, adam.foster@mclaren.org

**ABSTRACT**

FOSTER A, HERNANDEZ S. Hepatitis A: A Case Report Example of a Growing Epidemiological Threat. *Spartan Med. Res. J.* Vol. 3, No. 3, 2019. **CONTEXT:** Hepatitis A is a common worldwide cause of acute hepatitis. It has been classically associated with epidemics and is increasingly prevalent in the developing world. Generally, the illness is self-limited and only requires supportive management, reassurance, and proper hygiene instructions. **METHODS:** This case involves a male in his early 30s who presented non-emergently with jaundice and a weeklong history of fatigue, nausea, and flu-like symptoms. The patient underwent laboratory and radiological evaluation. **RESULTS:** Test results revealed a significant transaminitis, hyperbilirubinemia, and suggestion of cholecystitis. Further testing did reveal hepatitis A infection. **CONCLUSIONS:** This case illustrates the importance of clinicians having a high clinical suspicion for the disease based on individual risk factors as this disease can have a profound epidemiological impact in terms of local outbreaks and public health expenses. **Keywords:** hepatitis A, jaundice, epidemiology, public health

**INTRODUCTION**

Hepatitis is a generic term that refers to some manner of liver inflammation. The most common causes leading to such a diagnosis include viral infections and chronic alcohol abuse.1 Other causes can include bacterial, fungal, parasitic, immunologic, and toxic exposures. Hepatitis A Virus (HAV) is a virus that is spread almost exclusively through the fecal-oral route, although there does exist a very rare ability for blood transmission.1 HAV is an acute illness and there is no associated chronic carrier state (i.e., asymptomatic person capable of transmitting) such as seen with Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV). Typically, cases occur in association with epidemics,
as opposed to sporadic cases, with the most common risk factor for transmission being travel outside of the US.¹

The incubation period for HAV ranges from 14 to 45 days, with a relatively short duration of viremia (i.e., detectable virus in the blood) and maximum infectivity to others that is most prominent before symptom onset.¹ Differentiation of the cause of hepatitis generally requires a broad laboratory evaluation and thorough history and physical exam.

Although HAV is rarely diagnosed initially in the Emergency Department (ED) due to serology testing times,¹ a high clinical suspicion for the disease can lead to timely intervention including contact precautions and prevention of complications. Primary and secondary prophylaxis is available, however vaccination is not mandatory as the disease is rarely fatal, has no chronic carrier state, and has an overall low incidence in the United States.²

METHODS

Case Report

A Caucasian male in his early 30s presented to the ED with the chief complaint of yellowing of his skin and typically white sclera of his eyes. This was preceded by five days of progressive fatigue and flu-like symptoms. He also admitted to having produced several tan-colored bowel movements, dark urine, subjective fevers, and nausea. He denied any abdominal pain, vomiting, diarrhea, hematuria, or rashes. He also denied having completed any recent travel, insect or chemical exposures, or any known sick contacts.

He did not recall any peculiar food exposures during the prior week. He denied ever having experienced symptoms like this in the past but did admit to current HIV prophylaxis medication for the reason of “being smart.” He did admit to previous intravenous drug use with last administration three years prior. He had a history of mild well-controlled asthma and denied any previous surgeries.

The patient’s immediate vitals revealed hemodynamic stability with heart rate of 106, respiratory rate of 18, temperature of 97.6 degrees axillary, blood pressure of 140/86, and oxygen saturation of 100% on room air. His physical exam revealed a well-
nourished, diffusely jaundiced male in no acute distress. The patient was alert and oriented and answering all questions appropriately, albeit with short answers.

Further examination revealed prominent bilateral yellow discoloration of the eyes (i.e., scleral icterus) and abdominal examination demonstrated a mildly distended abdomen with mild tenderness in the right upper quadrant. There were no other indications of peritonitis and the remainder of the physical examination was within normal limits. The patient was provided with intravenous (IV) fluids and a broad laboratory evaluation and computerized axial tomography (CT) of the abdomen and pelvis with IV contrast was obtained.

CT of the abdomen and pelvis was interpreted as gall bladder contraction with wall edema and mucosal hyper-enhancement. (Figure 1) No gallstones were identified and the liver, common bile duct and pancreas were all within normal limits. Laboratory evaluation was obtained to evaluate for the degree of liver impairment and was pertinent for thrombocytopenia (88,000), hyperglycemia (451 mg/dL), hyperbilirubinemia (9.2 mg/dL), transaminitis (2238 U/L and 3806 U/L), and elevated PT-INR (i.e., prothrombin time-international normalized ratio) of 15.9 sec/1.54. (Table 1). These laboratory abnormalities suggested possible new-onset Diabetes Mellitus as well as significant liver dysfunction.

Given the radiological findings and suspicion for obstructive jaundice with possible gall bladder infection (i.e., cholecystitis), the authors discussed the case with general surgery. Orders for a magnetic resonance cholangiopancreatography (MRCP) and a viral hepatitis panel were placed for suspected concomitant acute hepatitis. The patient was initiated on IV antibiotics for suspected cholecystitis.

The case was then discussed with the Gastroenterology (GI) service who had also recommended a MRCP, avoidance of hepatotoxic medications (e.g., acetaminophen and ciprofloxacin) and hepatitis panel. The patient was subsequently admitted to the hospital in hemodynamically stable status with MRCP and hepatitis panel pending. Gastrointestinal (GI), general surgery and endocrinology for suspected new-onset Diabetes Mellitus were consulted on the case.

During the patient’s two-day hospital course, he underwent a MRCP which showed no gallstones (i.e., cholelithiasis), intra or extra-hepatic biliary dilatation,
choledocholithiasis, or pancreatic ductal dilatation. The patient’s newly diagnosed Diabetes Mellitus (Hemoglobin A1c of 9.2) was managed by Endocrinology. A hepatitis panel indicated no evidence of HBV or HCV reactivity but was reactive for anti-HAV immunoglobulin (IgM), suggesting acute HAV.

The patient was again evaluated by the same consulting services with further recommendations of no surgical intervention being required and trending of the hepatic function panel. On the patient’s hospital Day 2, his repeat hepatic function lab panel revealed improvement in the patient’s liver enzymes and function as well as his PT-INR. The patient was subsequently discharged after receiving medical clearance from the consultants with strict clinic-based follow-up. This entailed appropriate counseling with regards to risk factor modification as well as ensuring resolution of jaundice and viral shedding.

**DISCUSSION**

Patients affected by HAV can have a highly variable clinical presentation ranging from asymptomatic to fulminant (i.e., a severe sudden onset) liver failure. A significant number of those patients affected are actually asymptomatic, but malaise, fever, and anorexia are the most common presenting symptoms if they occur. These vague symptoms are generally followed by nausea, vomiting, diarrhea, abdominal discomfort, and the eventual development of jaundice. Fulminant HAV, on the other hand, is exceedingly rare occurring in only 1-2% of cases. This is characterized by hepatic failure and progressive encephalopathy (i.e., brain pathology) over a period of days.

Patients may also present with rare and specific symptoms as in this case including pale (i.e., acholic) stools and dark urine, both of which are indicative of a conjugated hyperbilirubinemia. This suggests an inability of the liver to expel bilirubin from the bile ducts, either from intrinsic hepatocyte dysfunction or an external obstruction or both. This is compared to an unconjugated hyperbilirubinemia that would typically suggest an abundance of bilirubin being produced for a myriad of reasons. Physical examination findings typically include scleral and/or cutaneous icterus, abdominal tenderness and palpable hepatomegaly. Aside from fever, other vital sign
abnormalities may be present, especially with concomitant vomiting, such as orthostatic hypotension and tachycardia.

When managing a patient presenting with jaundice and suspicion for hepatitis, it is especially important to gather a thorough history from the patient and their recent contacts if possible. This history should include any known sick contacts, travel history, illicit drug use, animal exposures, family history, or similar occurrences in the past. Any of these risk categories should lead clinicians to suspect some form of hepatitis as a cause of the patients’ presenting symptoms.

Clinicians being aware of current local epidemiological trends can also be of diagnostic benefit. As of the time of this writing, there had been a dramatic rise in the number of reported cases of acute HAV in Southeastern Michigan. The Michigan Department of Health and Human Services had reported that as of 3/21/18 (beginning 8/1/16) there have been 789 reported cases of HAV related to the outbreak.5 This condition contributed to 635 hospitalizations (80.5%) and 25 deaths (3.2%).

Of note, Macomb County has the highest number of reported cases at 212 cases which is more than the city of Detroit (i.e., 166 cases).5 The outbreak is believed to be linked to county-wide opioid and heroin use patterns as over half of the reported cases has some connection with this factor. As in this case, our patient admitted to a history of IV drug use and as was later determined during his hospitalization he also admitted to engaging in other high-risk behaviors including sex with other men.6

The economic impact of HAV outbreaks has been reviewed both globally as well as on a national level. One 2003 study in particular looked at a Spokane, Washington outbreak and estimated each case of HAV cost $2,683.7 Most of the expenditures were associated with hospital admissions and lost productivity in the community was also a major indirect factor. The expense of these endemics when compared to vaccination programs and other preventative public health initiatives continues to be an area of epidemiological interest.8

A HAV diagnosis is typically not made in the ED but suspected cases can be managed expectantly (i.e., monitored closely before treatment) while definitive studies are pending. The differential diagnosis includes bacterial, viral, fungal, parasitic, and alcoholic hepatitis.1 Also included are causes of extra-hepatic obstruction such as
cholelithiasis, cholecystitis, choledocholithiasis, and malignancy of the biliary and pancreatic tissue. Diagnostic imaging is usually indicated in the form of a right upper quadrant ultrasound and possible CT of the abdomen and pelvis.

More advanced imaging may be indicated in the form of a MRCP to further distinguish biliary pathology and possibly intervene on a cause of obstruction. The most critical laboratory studies to obtain include a hepatic function panel to assess degree of liver enzyme elevation (transaminitis), hyperbilirubinemia, and PT-INR which serves as the most accurate representation of hepatic impairment. Definitive studies for acute HAV (as well as HBV and HCV) can be obtained through a viral hepatitis panel. Acute HAV is indicated by positive Anti-HAV IgM whereas IgG indicates past exposure (when not co-existing with IgM).

Management of acute HAV includes IV fluids and electrolyte correction, antiemetics, and avoidance of hepatotoxic medications (e.g., acetaminophen and ciprofloxacin) and alcohol intake. Antiviral and antibiotic medications are not indicated in uncomplicated acute HAV. Hospitalization is generally reserved for those with intractable vomiting, severe electrolyte or fluid imbalance, altered mental status, a PT-INR greater than 1.5, or any other evidence of fulminant disease. Otherwise stable individuals can be safely discharged with a presumptive diagnosis and strict clinic-based gastroenterology follow-up. Patients should be instructed on strict hand hygiene and those working in the food industry should delay return to work until their jaundice has resolved.

According to the latest federal Centers for Disease Control (CDC) guidelines, unvaccinated persons who have been exposed recently to HAV should be administered one dose of the single-antigen HAV vaccine or immune globulin (IG) as soon as possible and within two weeks after exposure. IG is preferred for those less than 12 months old and greater than 40 years old, immunocompromised persons with chronic liver disease, and those who are allergic to the vaccine.

As for primary prophylaxis, the CDC and the Advisory Committee on Immunization Practices (ACIP) recommends that all children at one year of age, those at increased risk for infection or complications from HAV, and any person wishing to obtain immunity should receive the vaccination. The HAV vaccine has been available...
since 1995 and has resulted in a 95% decline in the incidence of disease. Despite the apparent success of the vaccine, mandatory administration is not the norm owing largely to the fact that the disease is rarely fatal, has no chronic carrier state, and has an overall low incidence in the United States.  

**CONCLUSIONS**

In this paper, the authors reported on the presentation of a patient with an acute HAV infection. A presumptive diagnosis of hepatitis was made in the ED based on the patient’s historical risk factors with symptomatology, coupled with supporting laboratory findings. The case was complicated by the findings on imaging suggestive of acute cholecystitis. Appropriate lab value serologies were obtained and supportive care was provided which resulted in a short hospital admission with gradual improvement in symptoms and liver function. This case illustrates the importance of clinicians observing a broader differential diagnosis as well as having an understanding of the illness course and possible complications. This case report example further stresses the significance of clinicians considering local epidemiological trends and how this may aid in diagnosis and appropriate management thereafter.

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The authors declare no conflict of interest.

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Accepted for publication December 2018
REFERENCES

## Table 1
Emergency Department Laboratory Evaluation

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<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
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<td>White Blood Cell (per µL)</td>
<td>4.09 x10^3</td>
<td>4.0-10</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>16.3</td>
<td>13-17</td>
</tr>
<tr>
<td>Platelets (per µL)</td>
<td>88 x10^3 (150-400)</td>
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</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>132</td>
<td>135-145</td>
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<tr>
<td>Potassium (mEq/L)</td>
<td>3.8</td>
<td>3.5-5</td>
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<td>Chloride (mEq/L)</td>
<td>95</td>
<td>95-105</td>
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<tr>
<td>Carbon Dioxide (mEq/L)</td>
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<td>20-29</td>
</tr>
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<td>HIV, Rapid Non-reactive</td>
<td></td>
<td></td>
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<tr>
<td>Blood Urea Nitrogen (mg/dL)</td>
<td>15</td>
<td>8-21</td>
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<td>Influenza A/B Negative</td>
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<td>Glucose (mg/dL)</td>
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<td>Creatinine (mg/dL)</td>
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<td>0.8-1.3</td>
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<td>Alkaline Phosphatase (U/L)</td>
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<td>Prothrombin/INR</td>
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<td>(11-14)/(0.9-1.2)</td>
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<td>Bilirubin, total (mg/dL)</td>
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<td>0.1-1.2</td>
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<td>Calcium (mg/dL)</td>
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<td>8.5-10.2</td>
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<td>Lactic Acid (mmol/L)</td>
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<td>Bilirubin, indirect (mg/dL)</td>
<td>1.42 (&lt;0.7)</td>
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<td>3806</td>
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<tr>
<td>Lipase (U/L)</td>
<td>193</td>
<td>10-150</td>
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Figure 1
CT Abdomen/Pelvis Axial Slice
Demonstrating Gall Bladder Contraction with Wall Thickening