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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Study

National preparedness survey of pediatric intensive care units with simulation centers during the coronavirus pandemic

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Abstract

BACKGROUND

The coronavirus disease pandemic caught many pediatric hospitals unprepared and has forced pediatric healthcare systems to scramble as they examine and plan for the optimal allocation of medical resources for the highest priority patients. There is limited data describing pediatric intensive care unit (PICU) preparedness and their health worker protections.

AIM

To describe the current coronavirus disease 2019 (COVID-19) preparedness efforts among a set of PICUs within a simulation-based network nationwide.

METHODS

based on your agreement to abide by the policies and procedures of The Indiana University Human Research Protection Program (HRPP).

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A cross-sectional multi-center national survey of PICU medical director(s) from children's hospitals across the United States. The questionnaire was developed and reviewed by physicians with expertise in pediatric critical care, disaster readiness, human factors, and survey development. Thirty-five children's hospitals were identified for recruitment through a long-established national research network. The questions focused on six themes: (1) PICU and medical director demographics; (2) Pediatric patient flow during the pandemic; (3) Changes to the staffing models related to the pandemic; (4) Use of personal protective equipment (PPE); (5) Changes in clinical practice and innovations; and (6) Current modalities of training including simulation.

RESULTS

We report on survey responses from 22 of 35 PICUs (63%). The majority of PICUs were located within children's hospitals (87%). All PICUs cared for pediatric patients with COVID-19 at the time of the survey. The majority of PICUs (83.4%) witnessed decreases in non-COVID-19 patients, 43% had COVID-19 dedicated units, and 74.6% pivoted to accept adult COVID-19 patients. All PICUs implemented changes to their staffing models with the most common changes being changes in COVID-19 patient room assignment in 50% of surveyed PICUs and introducing remote patient monitoring in 36% of the PICU units. Ninety-five percent of PICUs conducted training for donning and doffing of enhanced PPE. Even 6 months into the pandemic, one-third of PICUs across the United States reported shortages in PPE. The most common training formats for PPE were hands-on training (73%) and video-based content (82%). The most common concerns related to COVID-19 practice were changes in clinical protocols and guidelines (50%). The majority of PICUs implemented significant changes in their airway management (82%) and cardiac arrest management protocols in COVID-19 patients (68%). Simulation-based training was the most commonly utilized training modality (82%), whereas team training (73%) and team dynamics (77%) were the most common training objectives.

CONCLUSIONS

A substantial proportion of surveyed PICUs reported on large changes in their preparedness and training efforts before and during the pandemic. PICUs implemented broad strategies including modifications to staffing, PPE usage, workflow, and clinical practice, while using simulation as the preferred training modality. Further research is needed to advance the level of preparedness, support staff assuredness, and support deep learning about which preparedness actions were effective and what lessons are needed to improve PICU care and staff protection for the next COVID-19 patient waves.

Key Words: COVID-19; Pediatric intensive care unit; Simulation; Practice innovations; Training; Preparedness

Core Tip: The coronavirus disease 2019 pandemic has forced the United States healthcare system to examine the allocation of medical resources to the highest priority patients, including the pediatric population. In this cross-sectional multicenter national survey, we provide a description of the current preparedness efforts among a set of leading United States children's hospitals' pediatric intensive care units during the early months of the pandemic. This survey demonstrated that several key strategies have been implemented, including modifications to staffing, personal protective equipment usage, and workflows and changes in acute resuscitation and airway management, treatment protocols and procedures to limit personnel's exposure to the contagion, while using simulation as the preferred training modality.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has forced healthcare systems to examine the judicious allocation of scarce medical resources to the highest priority patients, including the pediatric population[1]. Recent studies report pediatric populations have a lower incidence and typically, a less severe presentation, as compared to adults[2]. Some children, particularly with co-morbidities, are more likely to develop critical illnesses such as respiratory and cardiac failure or shock that may require invasive respiratory support or extracorporeal hemodynamic support[3]. Recently, emerging data are suggesting, however, a more serious illness in kids, with hundreds of children sickened with severe illness due to COVID-19, now named multisystem inflammatory syndrome in children[4].

Diagnostic and therapeutic guidelines used for children are commonly extrapolated from studies conducted in adults. The Society of Critical Care Medicine published a national survey of more than 4500 intensive care specialists to assess adult intensive care unit (ICU) preparedness. This survey demonstrated that adult ICU settings are preparing for COVID-19 patient care by enacting a myriad of measures including: Preparing in-hospital non-ICU space, canceling elective surgeries, and preparing temporary spaces and external facilities[5]. Reviews of adult ICU preparedness for pandemics have focused on concepts of infection control and optimal ways to increase staffing and surge capacity[6]. Pediatric preparedness for COVID-19 is distinct from adult preparedness due to important physiological and equipment differences, distinct differences in pediatric COVID-19 presentations, the child's stage of development, and the intimate need for parent involvement as part of the care delivery model.

It is important to assess pediatric ICU preparedness to identify gaps and inform improvements as we prepare for present and future waves of the COVID-19 pandemic. Most children's hospitals in response to the pandemic have rapidly escalated their health systems preparedness and implemented innovative processes to prevent disease transmission and prepare their staff to care for COVID-19 patients[7,8]. Despite a widely accepted standard of care and national accreditation for pandemics and mass disasters for neonatal and pediatric critical care in the United States, recent data suggest that the United States system lacks adequate surge capacity and would benefit from a well-organized, nationally directed and cohesive approach[9,10].

There are limited data describing the extent of the actual changes implemented by pediatric ICUs (PICUs) and their approaches to improve pandemic their preparedness[11]. This survey aims to describe the current: (1) Preparedness efforts by a group of leading United States children's hospitals' PICUs; (2) Changes in policies/procedures /guidelines; and (3) Training modalities and innovations including use of simulation for COVID-19 care.

MATERIALS AND METHODS

Survey design

We conducted a cross-sectional multi-center national survey of PICU medical director(s) across children's hospitals in the United States. An established team of researchers designed and analyzed the survey. This survey was reviewed and approved by the local institutional review board at Indiana University Health.

PICUs

Thirty-five children's hospitals were identified for recruitment through an established national research network "Improving Pediatric Acute Care Through Simulation" (ImPACTS). The ImPACTS was founded in 2013 to improve the quality of care delivered to acutely ill and injured children and has conducted multiple research projects assessing the readiness of emergency departments through mixed methods research and simulation use[12]. The survey was conducted between May 2020 and June 2020. An anonymous Qualtrics survey (www.qualtrics.com) was distributed *via* e-mail to all lead investigators of 35 leading children's hospitals across the ImPACTS network. Each network site lead was instructed to e-mail the link to their PICU

medical directors and copy the study coordinator. Three e-mail reminders were sent by the study coordinator to the medical directors 1 week apart over a 3 weeks period.

Survey development

The questionnaire was developed and reviewed by physicians and researchers with expertise in pediatric critical care, disaster readiness, and survey development. The survey was pretested for length and comprehensibility at five different PICUs not included in the survey to improve the face validity (defined as whether or not the survey measures what it is supposed to measure) and the content validity (defined as the degree to which the survey is representative of the topic). The survey was iteratively revised in three cycles based on the feedback and pilot data.

The physician survey included 49 questions in multiple parts addressing six themes: (1) PICU and medical director demographics; (2) Pediatric patient flow during the pandemic; (3) Changes to the staffing models related to the pandemic; (4) Use of personal protective equipment (PPE); (5) Changes in clinical practice and innovations; and (6) Current modalities of training including simulation. An open comment section was available at the end of the survey.

Statistical analysis

We compared the frequencies and percentages responses by testing differences using the Fisher's exact test. A statistical review of the study was performed by a biomedical statistician. All reported *P* values are based on two-sided tests.

RESULTS

A total of 35 PICUs within the network were identified. Responses from 22 PICUs (63%) were received (Table 1).

PICUs and medical director characteristics

The majority of PICUs were located within children's hospitals, either in academic (64%) or community children's hospitals (23%). The geographic distribution of these hospitals within the United States was five (23%) in the West region, eight (36%) in the Northeast region, five (23%) in the Midwest region, and four (18%) in the southeast region. All PICUs (100%) cared for pediatric patients with COVID-19 at the time of the survey. Other key PICU characteristics are summarized in Table 1.

Changes in patients flow across PICUs

The majority of PICUs (83.4%) witnessed decreases in non-COVID-19 patient care. Forty-three percent had COVID-19 dedicated units, and 74.6% pivoted to accept adult COVID-19 patients (Table 2).

Changes in the staffing model

All PICUs in the survey (100%) implemented extensive changes to their staffing model. The most common changes were patient room assignment (50%), introducing remote patient monitoring (37%), and changes in their patient triage model (32%). The majority (90%) prohibited medical students from any direct patient care, while 50% and 32%, respectively, limited but did not prohibit residents and fellows from direct patient care (Table 2).

Use of PPE

The majority of PICUs (95%) conducted training for appropriate donning and doffing of enhanced PPE. The two most common educational formats were hands-on and video-based training (73% and 82%, respectively). Dedicated staff (spotter) were reported to be used only by 50% of the respondents. The majority (63.4%) of respondents reported they had dedicated zoning to distinguish clean areas from contaminated areas to reduce the likelihood that team members would cross over between areas leading to further contamination.

All PICUs developed and implemented procedures to enhance PPE practice safely and audit the competencies of their providers. The majority of PICUs (90%) conducted procedures to enhance the safety of enhanced PPE use. One-third of PICUs reported regular shortages of PPE (Table 3).

Table 1 Hospital pediatric intensive care unit characteristics

Characteristics of the pediatric intensive care units	*n* = 22 (%)
Primary hospital setting description	
Academic children's hospital	14 (63.64)[a]
Community children's hospital	5 (22.73)
Children's hospital with a combined pediatric/adult hospital	2 (9.09)
Other	1 (4.55)
Number of children's hospitals by bed capacity	
Less than 100	4 (18.18)
100-199	4 (18.18)
200-299	5 (22.73)
300-399	5 (22.73)
400+	4 (18.18)
PICU description	
Combined PICU/Cardiac ICU	6 (27.27)
PICU with a separate CICU at our institution	11 (50.00)
PICU only/ No CICU at our institution	5 (22.73)
Number of PICU beds per institution	
< 16	6 (27.27)
16-30	10 (45.45)
31-45	4 (18.18)
> 45	2 (9.09)
Number of patients with confirmed COVID admitted to PICUs	
1-3	13 (61.90)
4-6	1 (4.76)
7-9	4 (19.05)
> 10	3 (14.29)

[a]$P < 0.05$.

COVID: Coronavirus disease; CICU: Cardiac intensive care unit; ICU: Intensive care unit; PICU: Pediatric intensive care unit.

Practice changes and innovations

The most common concerns for PICU directors related to the changing COVID-19 treatment protocols and instituting new guidelines (50%) and shortage of PPE equipment and supplies (36%). The majority implemented changes in their airway management protocols (82%). The most common innovations were decreasing the number of team members in the patient room during resuscitation and incorporating new methods of communication (73% and 86%, respectively). Other innovations included using video laryngoscopy for intubation (68%) and implementing a COVID-19 specific airway management checklist. Sixty-eight percent of PICUs implemented changes in their cardiac arrest management of COVID-19 patients. Only 36% of PICUs implemented training for managing surge capacity. The most common methods for keeping PICU providers updated and best-prepared regarding COVID-19 preparedness activities were mass e-mail messaging or virtual meetings (91% and 77%, respectively) (Table 4).

Training modalities for COVID-19

Simulation-based training was the most commonly utilized training method (82%). The most common learning objectives were enhanced team training (73%) and improved team dynamics (77%). The majority of simulation occurred in the settings of

Table 2 Preparedness efforts of pediatric intensive care units

Changes in patient flow across PICUs	*n* (%)
Changes in the average non-COVID patients seen during the COVID season	
Increase in non-COVID patients	
Decrease in non-COVID patients	19 (83.4)[a]
No change	2 (9.52)
Presence of COVID dedicated unit(s)?	
Yes	9 (42.86)
No	12 (57.14)
Change in patients age range to include adult patients?	
Yes	10 (74.62)
No	11 (52.38)
Changes in the staffing model	
Implementation of changes to the healthcare provider staffing model	
Change in length of shift	4 (18.8)
Change in providers assignment for COVID-19 patients, dedicated teams	5 (22.73)
Change in patient triaging model	7 (31.82)
Change in room assignment	11 (50.00)
Introducing remote patient monitoring in PICU	8 (36.63)
Other	5 (22.73)
Limiting the exposure of medical trainees for patients with known or suspected COVID-19	
Fellows prohibited from direct patient contact	
Fellows limited but not prohibited from direct patient care	7 (31.82)
APPs students prohibited from direct patient	10 (45.45)
APPs students limited but not prohibited from direct patient care	1 (4.55)
Residents prohibited from direct patient care	5 (22.73)
Residents limited but not prohibited from direct patient care	11 (50.00)
Medical students prohibited from direct patient care	20 (90.91)[a]
Medical students limited but not prohibited from direct patient care	1 (4.55)
No changes	

[a]$P < 0.05$.

APPs: Advanced practice providers; COVID: Coronavirus disease; PICU: Pediatric intensive care unit.

patient care areas (77%). The majority of PICU directors felt that simulation was important to prepare better their PICU staff for COVID-19 patient management while protecting their staff from contamination. Simulation experts were the most common facilitators working within the department/hospital (68%). The most common challenges to increased simulation training were related to limited financial resources (32%) and securing adequate PPE (32%) (Table 5).

DISCUSSION

COVID-19 has placed extraordinary and sustained resource demands on critical care services. This survey provides a first snapshot of the current preparedness efforts among a set of leading PICUs in the United States during the first months of the pandemic. The majority of surveyed PICUs implemented dramatic changes to their workflow and adapted their staffing models, with 43% creating dedicated COVID-19

Table 3 Personal preparedness efforts by pediatric intensive care units

The use of PPEs	*n* (%)
Current issues/limitations in regards to the utilization of PPE	
Lack of access to PPE	
Shortage in PPE	7 (31.82)
Inability to reuse PPE	1 (4.55)
No issues	14 (63.64)
Conducting training to appropriately don and doff PPE for PICU staff	
Yes	21 (95.45)[a]
No	
Unsure	
Format of PPE training	
Hands-on training	16 (72.73)[a]
Video-based content	18 (81.82)[a]
Didactic/small group training	7 (31.82)
Email material	13 (59.09)
Other	2 (9.09)
Procedures to enhance safety of PPE	
Buddy system	8 (36.36)
Increased staff	6 (27.27)
Dedicated staff, spotter	11 (50.00)
Distribution of printed safety	13 (59.09)
Other	1 (4.55)
None	2 (9.09)
Auditing PPE competencies	
Assess the performance of doffing team	14 (63.64)
Written examination	
Simulation assessment	7 (31.82)
Provide structured feedback around key competency areas	4 (18.18)
Regularly assess competencies with spot checks and/or video	6 (27.27)
None	1 (4.55)
Optimization of PPE doffing areas	
Dedicated doffing area to avoid team members from bumping into one another or equipment	4 (18.18)
Zoning to distinguish clean area from potentially contaminated areas to reduce the likelihood that team members cross over between areas spreading contamination	8 (63.64)
Use the same space for donning and doffing of PPE	14 (63.64)
Dedicated staff to observe the doffing process, Doffing spotters	7 (31.82)
Other	5 (22.73)

[a]$P < 0.05$.

PICU: Pediatric intensive care unit; PPE: Personal protective equipment.

care units. Additionally, medical trainees with different professional backgrounds were either limited or prohibited from participating in direct patient care, posing significant workload burdens on PICU staff.

In March 2020, during the peak of the pandemic in New York City, The Association of American Medical Colleges and The Liaison Committee on Medical Education issued guidance that medical students should not be involved in the care of COVID-19 patients or persons under investigation, and many medical schools near the early epicenter of the pandemic discontinued clinical rotations[13]. Surveyed directors reported that they conducted extensive training on the proper use of enhanced PPE among their providers, while a third of surveyed programs reported regular shortages in PPE. Even 6 months into the pandemic, PPE shortages continue to be reported across the United States. Beyond this, more than two-thirds of PICUs implemented innovative training for their providers targeted at modified clinical practices for airway and cardiac arrest management, while only one-third implemented surge management training. Simulation conducted *in situ* is a well-established method for effective team training and was the most common training modality in our survey and was frequently utilized to support interprofessional team training and improve team dynamics in the ICU setting[14,15].

Our survey results are the first nationwide reports from pediatric ICUs with that have active simulation programs about their state of preparedness[7,16]. PICUs initiated rapid cycle planning and implementation of changes to established childcare models to ensure that safe and effective care was being maintained. Although many adult ICUs have reported on current approaches to improve preparedness, this is the first survey outlining the detailed preparedness steps and response efforts adopted by PICUs[17].

Many PICUs encountered a dramatic decrease in the number of non-COVID-19 patients as the pandemic evolved, which has likely helped balance the need for additional resources and training for all bedside providers to care for COVID-19 patients. In this survey, one-third of PICUs reported a consistent shortage in PPEs, which is similar to what has been reported in previous pandemics and which continues to put healthcare workers at risk[18-20]. This ongoing shortage of PPE is notable given the high risk of PICU staff exposed to aerosol-generating procedures, with recent data suggesting over 3000 healthcare workers have died caring for COVID-19 patients, including several intensive care providers, and at least 500000 healthcare providers reported infected worldwide[21,22].

The findings of the survey are a reflection of the overall preparedness efforts among the participating PICUs and the changes completed in operational policies by the surveyed PICUs. These changes translate into clinical and occupational benefits and can help in optimizing the clinical services of PICUs nationwide who are under resource constraints. These benefits include protecting healthcare providers and patients from the virus exposure to reduce the infection risks, establishing a community of practice among PICU clinical services and medical directors to avoid "reinventing the wheel" during the current pandemic, and more importantly identifying how best to prepare and implement more effective operational plans for predictable future pandemics. Furthermore, this survey serves as a guide to highlight and address present PICU system vulnerabilities. It supports PICU leadership and bedside providers in providing the highest quality of care and a laser-like focus on the safety of healthcare providers.

This survey has several limitations. While 22 of 35 major leading PICU medical directors responded, this represents only a sample of all United States PICUs, which may impact the generalizability of our findings. Additionally, this survey targeted PICUs that have active simulation programs, which may reflect more well-funded facilities. The survey, nonetheless, can provide deep insights into how PICU directors and programs are adapting their training, staffing, and workflow to address the ongoing, shifting pandemic demands. Additionally, the survey responses are inherently prone to bias and may not always accurately reflect the actual practice of clinical performance but rather the policies and intent. Lastly, we did not capture certain data such as the percent decrease in non-COVID-19 patients seen or visitors' policy to the PICUs.

CONCLUSION

We conclude in this first national survey that the current preparedness efforts among PICUs in the United States during the first few months of the COVID-19 pandemic

Table 4 Preparedness efforts by pediatric intensive care units

Practice change/Innovations	*n* (%)
Concerns related to the current COVID-19 clinical practice	
Lack of clinical guidelines/protocols	5 (22.73)
Changes in guidelines/protocols	11 (50.00)
Lack of PPE training	3 (13.64)
Physician staff shortage	
RN staff shortage	2 (9.09)
Other staff shortage	1 (4.55)
Shortage in equipment/supplies	8 (36.36)
Patient surge and crowding	5 (22.73)
Other	5 (22.73)
Implementation of COVID focused airway management training	
Yes	18 (81.82)
No	3 (13.64)
Unsure	
Practice innovations for airway management	
Caring for patients with suspected or confirmed COVID in negative pressure room	14 (63.64)
Using video laryngoscopy only for intubation	15 (68.18)
Decreased clinical care team numbers at bedside	19 (86.36)[a]
Incorporating new methods of communication between team members	16 (72.73)[a]
Implementing airway management checklists	15 (68.18)
Using telemedicine/video technology	9 (40.91)
Other	2 (9.09)
Intubation of suspected or confirmed COVID patients	
By anesthesiologist who responds as part of the Airway Team	5 (22.73)
Anesthesiologist or other dedicated airway provider who is called if intubation is required	7 (31.82)
Attending physician unless the patient is suspected of having a difficult airway	12 (54.55)
Attending physician or fellow	7 (31.82)
Any appropriately trained member of the team	
Other	8 (36.36)
Implementation of COVID focused cardiac arrest management training	
Yes	15 (68.18)
No	6 (27.27)
Unsure	
Practice innovations for cardiac arrest management	
Caring for patients with suspected or confirmed COVID in negative pressure rooms only	13 (59.09)
Changing CPR practices	10 (45.45)
Decreased clinical care team numbers at bedside	16 (72.73)[a]
Incorporating new methods of communication between team members	15 (68.18)[a]
Using telemedicine/video technology	7 (31.82)
Other	4 (18.18)
Implementation of surge capacity management training	

Yes	8 (36.36)
No	13 (59.09)
Unsure	
How does your PICU keep all providers updated regarding COVID preparedness activities?	
Mass e-mails	20 (90.91)[a]
Regular in-person huddle/meetings	11 (50.00)
Virtual conferences/meetings	17 (77.27)[a]
Simulation-based	9 (40.91)
Other	

[a]$P < 0.05$.

COVID: Coronavirus disease; CPR: Cardiopulmonary resuscitation; PPE: Personal protective equipment; PICU: Pediatric intensive care unit; RN: Registered nurse.

have been highly variable, with one-third lacking adequate PPE. PICUs have implemented several strategies including modifications to staffing and workflows, changes in their acute resuscitation and airway management, treatment protocols, limiting personnel's exposure to contagion, while using simulation as the preferred training modality to support protocol changes in response to COVID-19. Our findings highlight the importance of sharing experiences among PICUs, particularly during these challenging times. Future research is needed to better appreciate the effectiveness of better PPE preparedness, workflow, and training changes. We also need to better understand what are the impacts of limiting trainees' exposure to COVID-19 care on their clinical competencies in preparation for ongoing and future pandemics.

Table 5 Preparedness efforts by pediatric intensive care units

COVID-19 training modalities	*n* (%)
Modalities currently utilized for training staff?	
Video/teleconference	17 (7.27)
Didactic	12 (54.55)
Online modules	10 (45.45)
Simulation-based training	18 (81.82)
Virtual reality	1 (4.55)
Other	
Importance of simulation-based training for the preparation of PICU staff for COVID-19 patient management	
Extremely important	9 (40.91)
Important	7 (31.82)
Neutral	1 (4.55)
Unimportant	
Not at all important	
Objectives of the simulation-based training	
PPE, donning and doffing	12 (54.55)
Individual procedural skills, *i.e.* intubation	13 (59.09)
Team training, *i.e.* CPR	16 (72.73)
Team dynamics, *i.e.* communication	17 (77.27)
Mass casualty and surge capacity management	1 (4.55)
Diagnostic testing	1 (4.55)
Facility utilization and contingency planning, use of negative pressure rooms	2 (9.09)
Tent deployment	1 (4.55)
Other	
Location of the training	
Simulation center	3 (13.64)
In situ, in its original place or location	17 (77.27)
Classroom setting	
Other format, boot camp	1 (4.55)
Simulation equipment	
High-fidelity, full body mannequin, simulator	13 (59.09)
Low-fidelity, full body mannequin, simulator	7 (31.82)
Task trainers, intubation heads, central line trainers, *etc.*	7 (31.81)
Standardized patients, actors	1 (4.55)
Virtual Reality	3 (13.64)
Other	
Participating members	
Physicians	17 (77.27)
Nurses	17 (77.27)
Respiratory therapists	15 (68.18)
Technicians	5 (22.73)
Residents/fellows	15 (68.18)

Students	
Other staff	
What simulation training was the MOST helpful	
PPE, donning and doffing	6 (27.27)
Individual procedural skills, *i.e.* intubation	8 (36.36)
Team training, *i.e.* CPR	12 (54.55)
Team dynamics, *i.e.* communication	10 (45.45)
Other	1 (4.55)
What simulation training was the LEAST helpful	
PPE, donning and doffing	3 (13.64)
Individual procedural skills, *i.e.* intubation	2 (9.09)
Team training, *i.e.* CPR	2 (9.09)
Team dynamics, *i.e.* communication	2 (9.09)
Other	8 (36.36)
Facilitators of the simulation-based training	
Presence of a simulation center	7 (31.82)
Presence of a simulation team in your department/hospital	15 (68.18)
Buy-in/support from hospital administration team	8 (36.36)
Involvement in other simulation collaborative and simulation leadership	7 (31.82)
Other	8 (36.36)
Challenges to execute simulation-based training	
Buy-in/support from hospital administration team	1 (4.55)
Financial resources	7 (31.82)
Securing adequate supplies, PPE	7 (31.82)
Staff buy-in and participation	4 (18.18)
Lack of a trained simulation team	
Lack of simulation logistics/supplies	4 (18.18)
Lack of time for preparation	5 (22.73)
Lack of desire for this form of training	1 (4.55)
Other	7 (31.82)
Development of novel or unique training equipment or training aides	
Yes, *i.e.* intubating fume hood, please share	7 (31.82)
No	10 (45.45)

COVID: Coronavirus disease; CPR: Cardiopulmonary resuscitation; PICU: Pediatric intensive care unit; PPE: Personal protective equipment.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease pandemic caught many pediatric hospitals unprepared and has forced pediatric healthcare systems to scramble as they examine and plan for the optimal allocation of medical resources for the highest priority patients.

Research motivation

To help in optimizing the clinical services of pediatric intensive care units (PICUs) nationwide under resource constraints through a reflection of the overall preparedness efforts among a set of PICUs.

Research objectives

To describe the current coronavirus disease 2019 (COVID-19) preparedness efforts among a set of PICUs within a simulation-based network nationwide.

Research methods

A cross-sectional multi-center national survey of PICU medical director(s) across children's hospitals in the United States.

Research results

Responses from 22 of 35 PICUs (63%) were received. All PICUs cared for pediatric patients with COVID-19 at the time of the survey, and the majority witnessed decreases in non-COVID-19 patients. All PICUs implemented changes to their staffing models, and 95% of PICUs conducted training for donning and doffing of enhanced personal protective equipment. The majority of PICUs implemented significant changes in their airway management (82%) and cardiac arrest management protocols in COVID-19 patients (68%). Simulation-based training was the most commonly utilized training modality (82%), whereas team training and team dynamics were the most common training objectives.

Research conclusions

The current preparedness efforts among PICUs in the United States during the first few months of the COVID-19 pandemic have been highly variable. PICUs have implemented several strategies including modifications to staffing and workflows, changes in their acute resuscitation and airway management, treatment protocols, limiting personnel's exposure to contagion, while using simulation as the preferred training modality to support protocol changes in response to COVID-19.

Research perspectives

This survey highlights the importance of sharing experiences among PICUs, particularly during these challenging times, and how to prepare and implement more effective operational plans for predictable future pandemics.

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SYSTEMATIC REVIEWS

Vasopressin in vasoplegic shock: A systematic review

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Abstract

BACKGROUND

Vasoplegic shock is a challenging complication of cardiac surgery and is often resistant to conventional therapies for shock. Norepinephrine and epinephrine are standards of care for vasoplegic shock, but vasopressin has increasingly been used as a primary pressor in vasoplegic shock because of its unique pharmacology and lack of inotropic activity. It remains unclear whether vasopressin has distinct benefits over standard of care for patients with vasoplegic shock.

AIM

To summarize the available literature evaluating vasopressin *vs* non-vasopressin alternatives on the clinical and patient-centered outcomes of vasoplegic shock in adult intensive care unit (ICU) patients.

METHODS

This was a systematic review of vasopressin in adults (≥ 18 years) with vasoplegic shock after cardiac surgery. Randomized controlled trials, prospective cohorts, and retrospective cohorts comparing vasopressin to norepinephrine, epinephrine, methylene blue, hydroxocobalamin, or other pressors were included. The primary outcomes of interest were 30-d mortality, atrial/ventricular arrhythmias, stroke, ICU length of stay, duration of vasopressor therapy, incidence of acute kidney injury stage II-III, and mechanical ventilation for greater than 48 h.

RESULTS

A total of 1161 studies were screened for inclusion with 3 meeting inclusion criteria with a total of 708 patients. Two studies were randomized controlled trials

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and one was a retrospective cohort study. Primary outcomes of 30-d mortality, stroke, ventricular arrhythmias, and duration of mechanical ventilation were similar between groups. Conflicting results were observed for acute kidney injury stage II-III, atrial arrhythmias, duration of vasopressors, and ICU length of stay with higher certainty of evidence in favor of vasopressin serving a protective role for these outcomes.

CONCLUSION

Vasopressin was not found to be superior to alternative pressor therapy for any of the included outcomes. Results are limited by mixed methodologies, small overall sample size, and heterogenous populations.

Key Words: Vasopressins; Shock; Vasoactive agents; Treatment outcome; Vasoplegia; Arginine vasopressin

Core Tip: In this systematic review of vasopressin *vs* alternative vasoactive agents for the treatment of vasoplegic shock, vasopressin was not found to be superior to alternative pressor therapy for any of the included outcomes. However, results are limited by mixed methodologies, small overall sample size, and heterogenous populations.

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INTRODUCTION

Vasoplegic shock, one of the most significant complications that can arise after cardiac surgery, can be devastating and challenging to manage[1]. Vasoplegic shock is defined by low systemic vascular resistance despite adequate fluid resuscitation and a normal or increased cardiac index[2]. Post-operative vasoplegia is most common after cardiac surgery involving cardiopulmonary bypass, occurring in about 5% to 25% of patients[3]. While vasoplegic shock can occur after non-cardiac surgery[4], the most common risk factors for vasoplegia include cardiopulmonary bypass and the use of angiotensin converting enzyme inhibitors and beta blockers prior to surgery[1,5].

Vasoplegic shock involves both hyperactivity of vasodilatory pathways and resistance to and deficiency of common vasoconstrictor pathways[6,7]. Patients have been observed to mount a profound inflammatory response to cardiopulmonary bypass, leading to increased expression of nitric oxide synthase, decreased levels of vasopressin, and altered activity of catecholamine-sensitive secondary messenger systems[8,9]. Catecholamines, especially norepinephrine, have long been considered first line, but evidence supporting one therapy over another is limited and each carry the risk of adverse effects[10,11]. Other therapeutic agents targeting different pathophysiologic complications of vasoplegia include methylene blue, hydroxocobalamin, vasopressin, and angiotensin II and each carries distinct potential benefits and risks.

Vasopressin's unique pharmacology may lend it to being particularly beneficial in vasoplegic shock[12-15]. Activation of G_q-coupled vasopressin-1 (V1) receptors leads to smooth muscle contraction through the recruitment of intracellular calcium stores in the sarcoplasmic reticulum and extracellular calcium stores by opening L-type calcium channels[16,17]. There is also minimal V1 receptor expression in the pulmonary vasculature which may be of particular benefit to patients with right heart dysfunction or pulmonary hypertension[18]. Questions still remain, however, about its benefits over standard of care in shock. There is a lack of large, multi-center prospective trials addressing these questions. Thus, the aim of this systematic review was to summarize

the available literature evaluating vasopressin *vs* non-vasopressin alternatives on the clinical and patient-centered outcomes of vasoplegic shock in adult intensive care unit (ICU) patients.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2015 guidelines. A formal protocol does not exist for this systematic review.

Eligibility criteria

We included randomized controlled trials, prospective cohort studies, and retrospective cohort studies published in English in peer-reviewed journals. Studies were included if they studied adult patients (≥ 18 years), compared vasopressin to norepinephrine, epinephrine, hydroxocobalamin, or methylene blue, evaluated patients treated in the intensive care unit, and were suffering from post-operative vasoplegic shock. Follow-up needed to be until at least 30 d post-discharge. Studies needed to report 30-d mortality, acute kidney injury stage II-III based on Acute Kidney Injury Network classification (reference)[19], safety, ICU length of stay, mechanical ventilation duration, and duration of vasopressor therapy We excluded studies in pediatric patients, case reports, case series, review articles, letters, and notes. No restrictions were placed on the location of publication.

Data sources

A comprehensive search of several databases from each database's inception to December 6, 2019 of any language was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process and Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the reviewers. Controlled vocabulary supplemented with keywords was used to search for studies of vasoplegia/vasoplegic shock in critically ill patients. Actual strategy listing all search terms used and how they were combined is available in Supplementary 1.

Trial selection

Article titles and abstracts were screened by two independent authors (MOS and TN) for inclusion based on the aforementioned inclusion and exclusion criteria. The full text of articles included by title and abstract were then reviewed and disagreements were resolved through consensus.

Outcomes

The primary outcomes of interest were 30-d mortality, atrial/ventricular arrhythmias, vasopressor duration, stroke, ICU length of stay, proportion of patients suffering acute kidney injury, defined as acute kidney injury network stage 2 (serum creatinine [SCr] increase of 200% or urine output less than 0.5 mL/kg per hour in a 12 h period) or 3 (SCr increase of 300% or SCr greater than or equal to 4 mg/dL with an acute rise of at least 0.5 mg/dL or a urine output of less than 0.3 mL/kg/h in a 24 h period or anuria for 12 h)[19], and proportion of patients mechanically ventilated for greater than 48 h.

Methodological quality and certainty of evidence

The Cochrane Collaboration tool for assessing risk of bias was utilized to assess the quality and bias risk of included randomized controlled studies[20]. The tool assesses studies based on randomization, protocol deviation, missing outcome data, outcome measurements, and result reporting. The Newcastle Ottawa scale was used for assessing the risk of bias in observational studies[21]. The tool assesses studies based on selection methods, comparability, and outcome measurements. Discrepancies in scoring were resolved through consensus.

Data extraction

Two independent authors (MOS and TN) reviewed and extracted relevant data from included manuscripts in a standard data collection form. Collected data included publication information, protocol details, outcome measures, baseline characteristics,

and results.

Data analysis

For continuous outcomes, we gathered means and variance data [*e.g.*, standard deviation, standard error, confidence interval (CI)] and the weighted mean difference (MD). For binary outcomes, we gathered incidence data and frequencies and calculated the relative risk (RR). All statistical analyses were performed using R Core Team version 4.0.0 (2020).

RESULTS

Trial inclusion

The initial search identified 1161 studies. Following removal of duplicates and excluded records, 115 full-text articles were assessed for eligibility. Three (2.6%) of these met the inclusion criteria and were included in the analysis[23-25]. The results of the systematic search are summarized in Figure 1.

Trial characteristics

Of the 3 included studies, 2 were randomized controlled trials[24,25] and 1 was a retrospective cohort study[23]. A total of 1496 participants were included across the 3 studies (Table 1). The included studies were performed in Egypt, China, and Brazil, and publication dates spanned from 2016 to 2018. Characteristics of all of the included studies are detailed in Table 1.

Risk of bias

Overall, the risk of bias of the 2 included trials was moderate due to having some concerns in the randomization process of the 2 clinical trials[24,25]. The risk of bias for the cohort study was low[23]. The risk of summary bias is provided in Tables 2 and 3.

Outcomes

The results of included studies and the certainty of evidence are presented in Table 4 and Supplementary 2.

Thirty days mortality: Two studies were identified which reported 30-d mortality (n = 668)[23,24]. The risk of 30-d mortality was not found to differ between vasopressin as compared with norepinephrine.

Atrial/ventricular arrhythmias and stroke: Only two of the included studies reported safety events (n = 668)[23,24]. Although arrhythmias including atrial fibrillation and ventricular tachycardia occurred at a significantly higher frequency with vasopressin than norepinephrine as reported by Cheng *et al*[23] the certainty of evidence was low due to study design and imprecision. Hajjar *et al*[24] reported a similar frequency of ventricular tachycardia between the two pressors and vasopressin demonstrated a favorable profile at reducing atrial fibrillation when compared to norepinephrine. The certainty of evidence in these results was moderate. Although, neither study reported maximum dosage of study drug infusion rate, or dosage of vasopressors at the time of arrhythmia. Both studies did not report any differences in stroke.

Duration of vasopressors: Two studies reported duration of vasopressors (n = 668)[23,24]. The studies report discordant effect with one favoring use of vasopressin (MD -23, 95%CI -36.12, -9.88; moderate certainty of evidence, Hajjar *et al*[24]), while the other favoring use of norepinephrine (MD 24, 95%CI 16.32, 31.68; very low certainty of evidence, Cheng *et al*[23]).

ICU length of stay: All three studies reported ICU length of stay, although one study utilized methylene blue as the comparator (n = 40)[25], whereas the other two utilized norepinephrine (n = 668)[23,24]. No differences between vasopressin and methylene blue were found. When vasopressin was compared to norepinephrine, the two studies reported contradictory results with a longer length of stay in Cheng *et al*[23] (low certainty of evidence) and a shorter length of stay in Hajjar *et al*[24] (moderate certainty of evidence).

Acute kidney injury: Two studies reported incidence of acute kidney injury stage 2 or 3 (n = 668)[23,24]. Cheng *et al*[23] reported that vasopressin did not significantly affect the risk of acute kidney injury (very low certainty of evidence) while Hajjar *et al*[24]

Table 1 Trial characteristics

Ref.	Inclusion criteria	Exclusion criteria	Interventions (number of patients)	Age (yr)	Main outcomes
El Adawy *et al*[25], 2015	Severe sepsis diagnosed within 72 h and septic shock diagnosed within 24 h from the time of giving norepinephrine dose of greater than or equal to 0.2 μg/kg per minute, which is required to maintain the mean arterial pressure between 70 and 90 mmHg	(1) Pregnant females; (2) Patients sensitive to Methylene blue or vasopressin; (3) Patients with known G6PD deficiency; (4) Age less than 18 yr; (5) Vasospastic diathesis (*e.g.*, Raynaud's syndrome); (6) Coronary artery disease; and (7) Patients receiving mono amine oxidase inhibitors	Methylene blue (20); vasopressin (20)	55.3 ± 20.9; 59.4 ± 14.5	ICU length of stay; mean arterial pressure; central venous pressure; pulmonary artery pressure
Cheng *et al*[23], 2018	Patients with age more than 18 yr, who had left ventricular ejection fraction ≤ 35%, left ventricular end-diastolic diameter ≥ 60 mm, and New York Heart Association ≥ III), and developing postoperative vasoplegic shock (mean arterial pressure < 65 mmHg resistant to fluid challenge and cardiac index > 2.20 L/min per meter squared)	(1) Patients with chronic obstructive pulmonary disease; and (2) Adult congenital heart disease	Norepinephrine (938); vasopressin (218)	59.43 ± 11.07; 59.25 ± 12.73	30-d mortality; mechanical ventilation more than 48 h; cardiac reoperation; postoperative extracorporeal membrane oxygenation; stroke; acute kidney injury stage II/III; infection; septic shock; atrial fibrillation; ventricular arrhythmias
Hajjar *et al*[24], 2017	All adult (more than 18 yr of age) patients who were scheduled for coronary artery bypass graft surgery, valve replacement, or repair surgery with cardiopulmonary bypass who required vasopressor drugs for vasodilatory shock within 48 h after coronary artery bypass surgery weaning	(1) Aortic surgery; (2) Heart transplantation; (3) Preoperative use of vasopressor therapy; (4) Presence of a ventricular assist device other than an intra-aortic balloon pump; (5) Severe hyponatremia (< 130 mEq/L); (6) Acute coronary syndrome; (7) Acute mesenteric ischemia; (8) History of Raynaud disease; (9) Pregnancy; and (10) Neoplasm	Norepinephrine (151); vasopressin (149)	55 ± 13; 54 ± 14	Days alive and free of organ dysfunction at 28 d; stroke; acute renal failure; 30 d incidence of infection, septic shock, arrhythmias (atrial fibrillation and ventricular arrhythmias); duration of mechanical ventilation; changes in hemodynamic variables; the use of dobutamine or other vasoactive agents); incidence of digital ischemia; acute mesenteric ischemia; acute myocardial; infarction; ICU and hospital lengths of stay

G6PD: Glucose-6-phosphate dehydrogenase; ICU: Intensive care unit; mEq/L: Milliequivalents per liter.

Table 2 Risk of summary bias (randomized controlled trials)

Ref.	Overall ROB	ROB from randomization process	ROB due to deviations from intended interventions	ROB due to missing outcome data	ROB in measurement of outcomes	ROB in selection of the reported results	Other (funding, conflict of interest)
El Adawy *et al*[25], 2016	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk
Hajjar *et al*[24], 2017	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk	Low risk

ROB: Risk of bias.

demonstrated a considerable reduction in the risk of acute kidney injury when compared to norepinephrine (moderate certainty of evidence). Not enough data in the studies were available to assess need for or eventual dialysis dependency.

Mechanical ventilation > 48 h: Two studies reported outcome data on mechanical ventilation > 48 h (n = 668)[23,24]. Although not significant, vasopressin was associated with less episodes of mechanical ventilation lasting more than 48 h.

DISCUSSION

In this systematic review of the literature evaluating the role of vasopressin in the

Table 3 Risk of summary bias (cohort study)

Ref.	Overall ROB	Selection	Ascertainment of exposure	Comparability	Ascertainment of outcome	Adequacy of follow up
Cheng *et al*[23], 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

ROB: Risk of bias.

Table 4 Trial outcomes

Comparison	Vasopressin *vs* norepinephrine		Vasopressin *vs* methylene blue
Study	Hajjar *et al*[24], 2017	Cheng *et al*[23], 2018	El Adawy *et al*[25], 2016
Study design	Randomized trial	Cohort	Randomized trial
Sample size	330	338	40
30-d mortality	RR 0.97, 95%CI 0.57, 1.64; moderate	RR 3.33, 95%CI 0.93, 11.90; very low	-
Ventricular arrhythmia	RR 0.86, 95%CI 0.54, 1.35; moderate	RR 1.75, 95%CI 1.11, 2.76; very low	-
Duration of vasopressors	MD -23.00 d, 95%CI -36.12, -9.88; moderate	MD 24 d, 95%CI 16.32, 31.68; very low	-
Intensive care unit length of stay	MD -1.00 d, 95%CI -1.69, -0.31; moderate	MD 1.00 d, 95%CI 0.53, 1.47; low	MD 1.60 d, 95%CI -0.29, 3.49; very low
Stroke	RR 1.01, 95%CI 0.26, 3.98; low	RR 0.50, 95%CI 0.13, 1.97; very low	-
Acute kidney injury stage II/III	RR 0.32, 95%CI 0.21, 0.49; moderate	RR 1.12, 95%CI 0.89, 1.42; very low	-
Atrial arrhythmia	RR 0.78, 95%CI 0.67, 0.89; moderate	RR 1.70, 95%CI 1.02, 2.83; low	-
Mechanical ventilation > 48 h	RR 0.62, 95%CI 0.27, 1.46; low	RR 0.95, 95%CI 0.63, 1.42; very low	-

Data is presented as effect size, 95% confidence interval (CI), certainty of evidence. CI: Confidence interval; MD: Mean difference; RR: Relative risk.

treatment of post-operative vasoplegic shock, studies evaluating the effects on 30-d mortality, acute kidney injury stage 2-3, ICU length of stay, atrial fibrillation, ventricular arrhythmias, mechanical ventilation duration, and stroke were summarized. Meta-analysis was not feasible due to differences in methodology, patients, and procedures that led to variation in the reported results between studies.

Interest in vasopressin as treatment for vasoplegic shock has existed for a number of years due to its unique pharmacology independent of the autonomic nervous system. Current available literature, however, has been limited by small sample sizes, inconsistent populations, and varied outcomes, which has limited its use to adjunctive therapy. Insights from investigation into vasopressin's role in the treatment of septic shock, however, may supplement knowledge on vasopressin's role in vasoplegic shock. Randomized controlled trials of vasopressin in septic shock have not revealed a significant mortality benefit, but signals of preserved renal function, decreased overall pressor requirements, and largely equitable safety outcomes has changed it from salvage therapy to standard care for many patients with septic shock[26-30].

The evolution of vasopressin in septic shock may foreshadow the role of vasopressin in vasoplegic shock. Norepinephrine and epinephrine have functioned as the workhorses of vasoplegic shock management for decades and clinical experience outweighs the influence of the available literature to support the role of vasopressin. As clinical experience with vasopressin grows alongside the expansion of the literature, vasopressin utilization in vasoplegic shock without cardiogenic shock will likely increase. The results of this systematic review did not reveal any major advantages to vasopressin use but highlight the need for robust investigation into many of these outcomes.

Like other studies investigating specific pressors, 30-d mortality was not found to be different between patients who received vasopressin or norepinephrine in our systematic review. This is concordant with studies evaluating pressors in other shock states as well as studies evaluating vasopressin in septic shock. Few large randomized controlled trials have succeeded in demonstrating a reduction in mortality of a

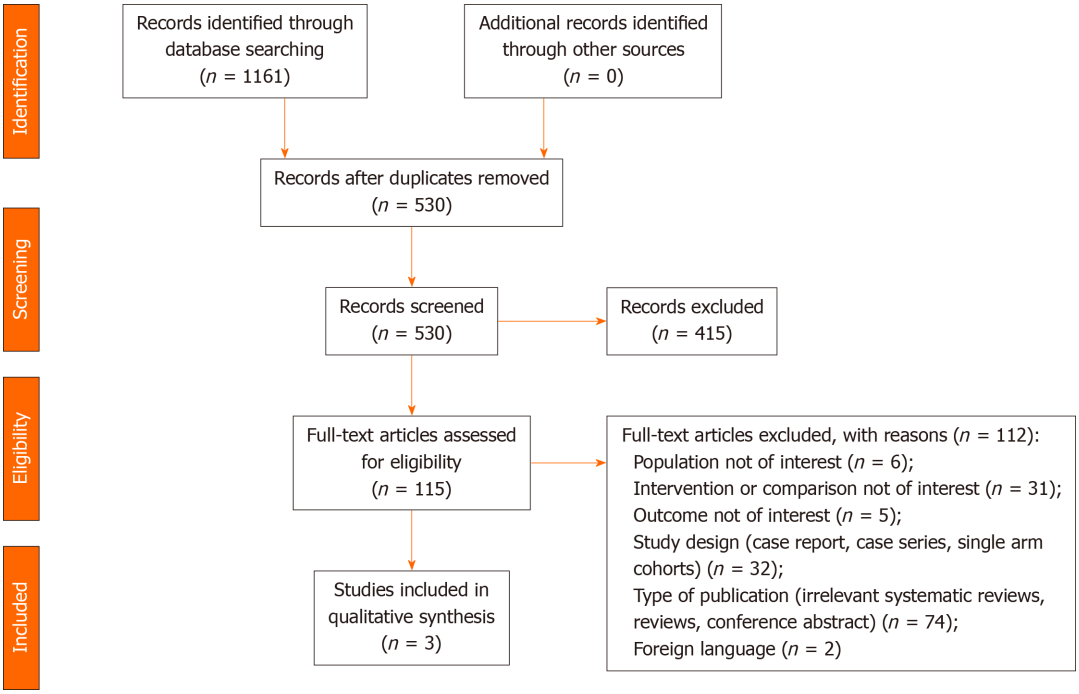

Figure 1 Study flow diagram.

singular critical care intervention, and the benefit of each individual intervention, such as the choice of vasopressor, may be better judged by its incremental benefits on morbidity and patient-specific outcomes[31-33].

No difference was revealed in ICU length of stay for vasopressin compared to norepinephrine or methylene blue in our systematic review. Of note, opposing results were reported in Hajjar *et al*[24] and Cheng *et al*[23] This imbalance may in part be due to the different baseline populations in each study, with Hajjar *et al*[24] excluding patients with left ventricular dysfunction and Cheng *et al*[23] specifically including these patients, as well as the study design (randomized clinical trial *vs* cohort study). In a meta-analysis of vasopressin in septic shock, vasopressin has not been reported to have a significant impact on ICU length of stay (mean different -0.08 d, 95%CI -0.68, 0.52)[34].

Vasopressin was not found to impact rates of stroke in patients with vasoplegic shock. Perioperative stroke after cardiac surgery is uncommon, estimated to occur in about 2% of all patients after surgery, but rates of mortality after perioperative stroke are much higher than the overall population[35,36]. While our findings indicate choice of pressor did not influence this risk, the overall sample size may be too low to estimate the impact on a rate outcome (combined event rate was 17). Potential confounders for risk of stroke, such as previous stroke, were not reported.

Given its lack of autonomic activity, one potential benefit of vasopressin is its presumed lack of arrhythmogenic properties. In our analysis, we found conflicting results from the two studies which reported ventricular and atrial arrhythmias as an outcome. This finding contrasts that of a patient-level meta-analysis of adverse event data in septic shock, which found vasopressin was associated with an absolute risk reduction of 2.8% (95%CI -0.2, -5.3) in rates of arrhythmia compared to norepinephrine[26]. Vasopressin with a catecholamine was also found to confer a lower risk of atrial arrhythmia compared to catecholamines alone in a meta-analysis of multiple shock states (RR 0.77, 95%CI 0.67, 0.88)[37]. The different results of each study in our systematic review are potentially driven by the unreported doses of pressors in Cheng *et al*[23] at the time of ventricular arrhythmia onset and the higher vasopressor needs overall in the six hours after cardiac surgery in the vasopressin group, which would be an unaccounted confounder. Of note, one should be aware that the randomized clinical trial, Hajjar *et al*[24], demonstrated reduced arrhythmogenic potential for both atrial and ventricular arrhythmias with vasopressin compared to norepinephrine unlike the cohort study of Cheng *et al*[23].

The two studies reporting vasopressor duration also had opposite effects. This discrepancy is likely due to differences in methodology and patient populations between the two studies. Considering the heterogeneity between these two studies

(see Supplementary 2) and the overall higher level of evidence in Hajjar *et al*[24], the beneficial effect on vasopressor duration in Hajjar *et al*[24] is likely a better representation of the true effect of vasopressin on this outcome, as we demonstrate for the arrhythmia and renal endpoints. Duration of vasopressor therapy may be better reported as days alive and free of vasopressors, a more patient-centered outcome[38].

Rates of stage II or III acute kidney injury were not found to be different depending on which pressor was used for vasoplegic shock. Vasopressin has unique activity at the glomerulus, including an ability to selectively constrict the efferent arteriole and not the afferent arteriole, leading to an observed increase in urine output in patients with septic shock[14,39]. In a meta-analysis of multiple shock states, vasopressin was revealed to be protective for acute kidney injury compared to alternative therapy (OR 0.52, 95%CI 0.32, 0.86). This analysis, however, is limited by mixing definitions of acute kidney injury, study designs, and indications. Need for renal replacement therapy was also not protocolized and up to the decision of the treating provider, making it difficult to compare rates between studies.

Choice of vasopressor did not impact rates of prolonged (greater than 48 h) mechanical ventilation. These results mirror other meta-analyses of patients with septic shock, where duration of mechanical ventilation (MD -0.58 h, 95%CI -1.47, 0.31) or number of ventilator-free days (13 *vs* 13) was not different between vasopressin and other pressors[26,34].

This systematic review has several limitations which should be highlighted. A large portion of our literature search met exclusion criteria because of study design or intervention which limits the sample size available for analysis. Of the studies included, only two reported many of the outcomes of interest, further limiting sample size. The studies also differ in methodology and risk of bias, making comparison of results between studies more challenging. There was also significant variation in dosing strategies of vasopressin and the reporting of concurrent vasopressor therapy which likely impacted results. This, combined with the heterogeneity revealed between the studies, reduce the reliability of the reported results.

CONCLUSION

Patients who experience vasoplegic shock suffer from significant morbidity and mortality and identification of optimal treatment modalities is of paramount importance to clinicians caring for these patients. Given its unique pharmacology, vasopressin may play a role as optimal therapy in certain patients with vasoplegic shock but should be considered as adjunct in all patients refractory to catecholamines. While current literature is promising, several questions still remain about vasopressin, such as ideal dosing strategies, timing of initiation, and in which patient populations vasopressin as a primary pressor may be ideal. Additional prospective multi-center research is warranted to investigate vasopressin's role in improving patient-centered outcomes of post-operative vasoplegic shock on a large scale.

ARTICLE HIGHLIGHTS

Research background

Vasoplegic shock is a devastating complication post-surgery, in particular cardiac surgery, that leads to poor patient outcomes. Currently, treatment for this condition consists of norepinephrine and epinephrine. However, because of vasopressin's unique pharmacology, it may have a role in the treatment of this condition.

Research motivation

Effective therapies aimed at hemodynamic preservation have not been identified in vasoplegic shock. Although norepinephrine and epinephrine are routine management, they have not proven all that effective for this condition given their hemodynamic profile and association with other complications. Vasopressin with its unique pharmacology and beneficial association with certain patient centered outcomes may be a reasonable first line alternative.

Research objectives

The aim of this systematic review was to summarize the available literature evaluating vasopressin *vs* non-vasopressin alternatives on patient-centered outcomes of

vasoplegic shock in adult intensive care unit (ICU) patients. The aim of the present study will provide useful information on whether vasopressin maybe beneficial in the treatment of vasoplegic shock.

Research methods

Randomized controlled trials, prospective cohorts, and retrospective cohorts comparing vasopressin to norepinephrine, epinephrine, methylene blue, hydroxocobalamin, or other pressors were included. The primary outcomes of interest were 30-d mortality, atrial/ventricular arrhythmias, stroke, ICU length of stay, duration of vasopressor therapy, incidence of acute kidney injury stage II-III, and mechanical ventilation for greater than 48 h. Given the mixed methodologies and heterogenous populations of the included studies and the overall small sample size, a meta-analysis was not conducted. We present weighted mean difference for continuous outcomes and relative risk for binary outcomes with associated confidence intervals.

Research results

A total of 1161 studies were screened for inclusion with 3 meeting inclusion criteria with a total of 708 patients. Two studies were randomized controlled trials and one was a retrospective cohort study. Primary outcomes of 30-d mortality, stroke, ventricular arrhythmias, and duration of mechanical ventilation were similar between groups. Conflicting results were observed for acute kidney injury stage II-III, atrial arrhythmias, duration of vasopressors, and ICU length of stay with higher certainty of evidence in favor of vasopressin serving a protective role for these outcomes. Although our results do not provide conclusive evidence of a beneficial role for vasopressin in the treatment of vasoplegic shock, we do provide some rationale as to why vasopressin could have a protective effect with regards to certain patient centered outcomes such as acute kidney injury, atrial arrhythmias, *etc*. We also provide some direction for future research in this area.

Research conclusions

Vasopressin was not found to be superior to alternative pressor therapy for any of the included outcomes. Results are limited by mixed methodologies, small overall sample size, and heterogenous populations. We identify limitations in the present systematic review such as mixed methodologies and heterogeneous populations that preclude a definitive answer on the role of vasopressin in vasoplegic shock. Future studies should have more homogenous populations with similar methodologies so that a pooled analysis can be performed to definitively answer this question.

Research perspectives

While current literature is promising, several questions still remain about vasopressin, such as ideal dosing strategies, timing of initiation, and in which patient populations vasopressin as a primary pressor may be ideal. Additional prospective multi-center research is warranted to investigate vasopressin's role in improving patient-centered outcomes of post-operative vasoplegic shock on a large scale taking into consideration dosing strategies and timing of initiation of vasoactive agents.

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