Proactive vs. Reactive Approach to Vasovagal Reactions during Erythrocytapheresis

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Author: Eleanor Pineda

EBP Mentors: Amanda Davis, MPH, RD, CHES, Rebecca Harper, Emily Brennan MLIS

ASK THE QUESTION

Clinical Question: What measures should be taken to minimize or prevent vasovagal reactions associated with Erythrocytapheresis or Isovolemic Hemodilution Red Cell Exchange Therapy

Objective: To minimize or prevent vasovagal reactions during or after Isovolemic Hemodilution Red Cell Exchange Therapy

Background: Red Blood Cell Depletion Exchange is being used more frequently because it reduces a Sickle Cell patient’s Hgb S more effectively than other therapies. However, vasovagal reactions are one of the associated adverse effects due to the fluid shifts that occur during treatment. There have been at least 5 occurrences of vasovagal reactions associated with Isovolemic Hemodilution Red Cell Exchange Therapy this year in our department. The symptoms associated with vasovagal reactions (lightheadedness, diaphoresis, hypotension, loss of consciousness) cause anxiety and fear to the patients, compromise patient safety, increase length of time in the unit, interrupt the unit’s schedule, and possibly result in admittance to the Emergency Department.

SEARCH FOR EVIDENCE

Databases searched: included PubMed, CINAHL, and SCOPUS

Search strategies (list strategy for each database): included (vasovagal or syncope or fainting) and (Erythrocytapheresis or Red Cell Exchange or Isovolemic Hemodilution Red Cell Exchange Therapy) ; Vasovagal reactions and Apheresis, hydration and vasovagal reactions

Filters/limits applied: relevance, research articles in English

Insert narrative summary of articles in your GRADE table and any pertinent guideline recommendations (including quality of evidence, if provided).
<table>
<thead>
<tr>
<th>Author/Date/ Journal</th>
<th>Purpose of Study</th>
<th>Study Design</th>
<th>Sample and Setting</th>
<th>Outcomes</th>
<th>Design Limitations</th>
</tr>
</thead>
</table>
| Fisher et. al., 2016, British Blood Transfusion Society | The World Health Organization recommended that both predonation hydration and applied muscle tension be employed to reduce the incidence of vasovagal reactions. This study presents a systematic review of the interventions designed to prevent or reduce vasovagal reactions in blood donors. | Systematic review and Meta-analysis | • Healthy blood donors (standard unit whole blood, double dose red blood cell and platelet donors) with any intervention designed to prevent or reduce Vasovagal reactions  
• 5 trials with 12,042 participants of predonation water  
• 8 trials with 3500 participants of applied muscle tension | • Donors who consumed water prior to donation had significantly lower risk of experiencing VVR than those who were not given water (RR 0.79, 95%CI 0.70-0.89; P<0.0001)  
• No difference in risk of pre-syncopal reactions in donors who performed applied muscle tension compared with controls  
• Combined hydration and applied muscle tension | Study Limitations  
Insufficient Sample Size |

**Studies are indirect because it different from actual PICO question from the available evidence in regard to population and setting.**

**Level of evidence for studies as a whole:**

Moderate
<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Method</th>
<th>Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanson and France, 2004, Transfusion</td>
<td>To study the effect of predonation water ingestion on negative physiologic reactions to blood donation. This study derived from evidence that showed that ingesting 500mL of water increased sympathetic activation, vascular resistance, and blood pressure and from a recent study that indicated that consumption of 473mL of water significantly increased tolerance of upright posture during a head tilt test.</td>
<td>Randomized Controlled Trial</td>
<td>• 1 trial each of applied muscle tension combined with water, caffeine, audio-visual distraction and/or social support; applied muscle tension showed significant reduction in frequency of VVR but were inconclusive due to limited sample size</td>
<td>Study limitations= limited sample size</td>
</tr>
<tr>
<td>Fisher et al., 2016, British Society Blood Transfusion</td>
<td>The aim of this study was to identify possible risk factors for donor reactions related to pediatric procedures undergone by children.</td>
<td>Systematic review of predonation intervention studies</td>
<td>• Study derived from evidence that ingestion of 500mL of water was associated with 47% reduction of total donation related symptoms; Study derived from evidence that ingestion of 500mL of water was associated with 47% reduction of total donation related symptoms and from a recent study that indicated that consumption of 473mL of water significantly increased tolerance of upright posture during a head tilt test.</td>
<td>Study limitations= Insufficient sample size</td>
</tr>
</tbody>
</table>

**Table:**

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<th>Study Design</th>
<th>Study Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy donors</td>
<td>8 trials</td>
<td>Randomized Controlled Trial</td>
<td>Insufficient sample size</td>
</tr>
<tr>
<td>Predonation water ingestion</td>
<td>5 trials</td>
<td>Randomized Controlled Trial</td>
<td>Insufficient sample size</td>
</tr>
<tr>
<td>No water ingestion</td>
<td>5 trials</td>
<td>Randomized Controlled Trial</td>
<td>Insufficient sample size</td>
</tr>
</tbody>
</table>

**Legend:**
- VVR: Vasovagal reaction
- RR: Relative Risk
- PICO: Population, Intervention, Comparison, Outcome
- I²: Heterogeneity index
- *P*<0.0001: Highly significant

**Additional Notes:**
- The table includes studies that investigated the effect of predonation water ingestion on blood donation reactions, focusing on the incidence of vasovagal reactions, the frequency of VVR, and the effectiveness of interventions like muscle tension applied and distraction.
- Studies were evaluated for their level of evidence, study design, and potential limitations.
Michon et al., 2007, Transfusion  

The aim of this study was to describe the type and frequency of immediate and late adverse reactions related to pediatric aphaeresis. It also identified possible risk factors for complications.

| Cohort Study-retrospective | 186 children that had undergone 1632 aphaeresis procedures between 1994 and 2002  
• 25 out of 186 children had sickle cell anemia  
• Out of 1632, 6.9% were red blood cell exchanges | 55% of procedures in 82% of patients had adverse reactions reported  
• 14 (48.4%) Hypotension  
• 4.8 (26.9%) Hypotension on requiring fluid bolus  
• 9.7% (28.5%) symptomatic

Study limitations=Insufficient sample size
hypocalcemia
• Based on multivariate analysis risk factors for complications were lower body weight and lower apheresis hemoglobin level
• It found that in cases of hypotension a bolus of 0.9% NaCl or 5% Albumin 10-15mL/kg was given and the procedure interrupted until symptoms resolved
APPLY THE EVIDENCE

Practice Recommendation(s):
Proactive intervention like pre and post hydration, minimal post treatment bedrest of 30 minutes, applied muscle tension, proper nutrition prior to treatment needs to be implemented to minimize or prevent vasovagal reactions during or after treatment.

Strength of Recommendation: Strong
Quality of Evidence: Moderate

EVALUATE THE EVIDENCE

Outcome & Process Measures:
-implementation of pre and post treatment hydration either by po fluids or IVF of NS for patients about to undergo RBC Depletion/Exchange vs no implementation
-implementation of post treatment bedrest (supine) for at least 30 minutes post treatment versus no bedrest
-education of patient to hydrate at least 24 hours prior to treatment versus patient not complying
-vasovagal reaction rates

Implementation Plan:
-introduce implementation at next staff meeting after approval of medical attending
-patient education

REFERENCES

Appendix A: GRADE criteria for rating a body of evidence on an intervention
Developed by the GRADE Working Group

**Grades and interpretations:**
High: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low: Any estimate of effect is very uncertain.

**Type of evidence and starting level**
Randomized trial–high
Observational study–low
Any other evidence–very low

**Criteria for increasing or decreasing level**

**Reductions**
Study quality has serious (–1) or very serious (–2) problems
Important inconsistency in evidence (–1)
Directness is somewhat (–1) or seriously (–2) uncertain
Sparse or imprecise data (–1)
Reporting bias highly probable (–1)

**Increases**
Evidence of association† strong (+1) or very strong (+2)
Dose-response gradient evident (+1)
All plausible confounders would reduce the effect (+1)
†Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders. Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix B: U Penn’s Trustworthy Guideline rating scale
The University of Pennsylvania’s Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine’s “Standards for Developing Trustworthy Clinical Practice Guidelines” (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guideline does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Guideline development methods are fully disclosed.</td>
</tr>
<tr>
<td>B</td>
<td>Guideline development methods are partially disclosed.</td>
</tr>
<tr>
<td>C</td>
<td>Guideline development methods are not disclosed.</td>
</tr>
</tbody>
</table>

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:
Who wrote the initial draft
How the committee voted on or otherwise approved recommendations

Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

<table>
<thead>
<tr>
<th>Grade</th>
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</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).</td>
</tr>
<tr>
<td>B</td>
<td>Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.</td>
</tr>
<tr>
<td>C</td>
<td>Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.</td>
</tr>
<tr>
<td>NR</td>
<td>Guideline does not report on potential conflict of interests.</td>
</tr>
</tbody>
</table>

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

| A | Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties. |
| B | Guideline development group includes one of the above, but not both. |
| C | Guideline developers all from one specialty or organization, and no methodologists. |
| NR | Affiliations of guideline developers not reported |

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

| A | Guideline includes a systematic review of the evidence or links to a current review. |
| B | Guideline is based on a review which may or may not meet systematic review criteria. |
| C | Guideline is not based on a review of the evidence. |

In order to qualify as a systematic review, the review must do all of the following:
- Describe itself as systematic or report search strategies using multiple databases
- Define the scope of the review (including key questions and the applicable population)
- Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.

Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence
Specific supporting evidence (or lack thereof) for each recommendation is cited and graded.

Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.

Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

| A | Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form. |
| B | Either one or the other of the above criteria is met. |
| C | Neither of the above criteria are met |

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

| A | Guideline was made available to external groups for review. |
| B | Guideline was reviewed by members of the sponsoring body only. |
| C | Guideline was not externally reviewed. |
| NR | No external review process is described. |

8. Updating and currency of guideline

| A | Guideline is current and an expiration date or update process is specified. |
| B | Guideline is current but no expiration date or update process is specified. |
| C | Guideline is outdated. |

A guideline is considered current if it is within the developers’ stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst’s discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated.