A RABBIT VENOUS MODEL OF INFUSION INFILTRATION TO STUDY THE EFFECT OF A HYPEROSMOTIC SOLUTION

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Conflict of interest
Hidenori Tanabe is a collaborative researcher of the University of Tokyo and has been employed by TERUMO corporation (Tokyo, Japan). Naoto Takemura is also a research associate at TERUMO corporation. The other authors have been determined to have no conflict of interest.

Funding
This research was a joint project with Terumo corporation, conducted with sponsorship from this organization.
EVENTUAL GOAL

We would like to suggest the most suitable routes for the administration of a hyperosmotic solution through animal studies.
OUR PREVIOUS STUDY

- An observational study in a university hospital (2014)
- The rate of catheter failure (CF) was reported to be 30%.
- Used ultrasonography (US) to better understand the causes of CF.

(Takahashi et al. 2015)
OUR PREVIOUS STUDY

We classified US images detected in the study into four types of US features.

N=186 PIVC (145 subjects)

A: No signs; 51 PIVCs (25.5%)
B: Thrombus; 48 PIVCs (24.0%)
C: Subcutaneous edema; 30 PIVCs (15.0%)
D: Thrombus with subcutaneous edema; 57 PIVCs (28.5%)

We found no catheter dislocations in this study. Our results suggest that catheter failure could be caused by other reasons than catheter dislocation.

Figure 1. Typical US features (A-D)

(Yabunaka et al. 2015)

The mild echo spots in the vein show partial occlusion of the vein by thrombus. The area surrounding the vein with the PIVC tip appeared as an edema of the subcutaneous fat layer (circles). We could not evaluate 14 (7.0%) US images because of poor image quality.
Table 1. Rates of catheter failure (CF) with and without BFLUID®

<table>
<thead>
<tr>
<th></th>
<th>Rates of CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with BFLUID®</td>
<td>66% (25/38)</td>
</tr>
<tr>
<td>Patients without BFLUID®</td>
<td>22% (35/162)</td>
</tr>
</tbody>
</table>

CF was defined as accidentally removal of the catheter due to the signs, symptoms and insufficient dripping.

BFLUID® (845mOsm/L) has been commonly used in Japanese acute care hospitals for PPN in short time duration.

Infusion Nurses Society (INS) recommends that Central Venous Access Device (CVAD) is preferred for continuous infusion of hypertonic solution (osmolarity > 900mOsml/L).

(Policies and Procedures for Infusion Therapy, 2016)
**SYMPTOMS ASSOCIATED WITH HYPERTONIC SOLUTION**

What is the main symptom of CF in patients who received hypertonic solution?

Table 2. Rates of clinical presentation of CF in patients with BFLUID®

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Rates (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>64 % (16/25)</td>
</tr>
<tr>
<td>Pain</td>
<td>60 % (15/25)</td>
</tr>
<tr>
<td>Erythema</td>
<td>48 % (12/25)</td>
</tr>
<tr>
<td>Palpable venous cord</td>
<td>24 % (6/25)</td>
</tr>
</tbody>
</table>

Edema, which is the main symptom of CF, can be defined as infiltration based on the INS rating scale.
OUR PREVIOUS STUDY

Vessel diameter

To reveal any differences in mean diameter between veins with infiltration and those without infiltration, US was used.

Table 3. Vessel diameter with and without infiltration in patients receiving BFLUID®

<table>
<thead>
<tr>
<th></th>
<th>Infiltration</th>
<th>No-infiltration</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD), mm</td>
<td>Mean (SD), mm</td>
<td></td>
</tr>
<tr>
<td>Vessel diameter</td>
<td>1.3 (0.29)</td>
<td>2.6 (0.81)</td>
<td>.008</td>
</tr>
</tbody>
</table>

To clarify what’s happening in the vein, experimental studies using animal models are needed.

Short-axis sonographic image of a vein with inserted PIVC tip

Noblus
(Hitachi Aloka Medical)
Liner-array transducer
(5-18MHz)
HYPOTHESIS

Infiltration can be caused by mechanical, physiologic, or pharmacologic factors. (Hadaway, 2007)

Vesicant solutions can irritate the venous endothelium, allowing the solutions to escape from the gap of the vein into the surrounding tissue. (Pettit J, 1993)

Undemonstrated

Our hypothesis

Hyperosmotic solution causes the loss of vascular endothelial cells, which leads to the passage of fluid (= edema defined as infiltration).

Specific observation of venous endothelium is needed.
Rabbit ear vein has usually been used for investigations of infusion complications. (Kuwahara T. 1998)

Fig. 1. Infusion technique and sampling regions for histopathological examination.

Table 3. Criteria for histopathological examination.

<table>
<thead>
<tr>
<th>Histopathological findings</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of venous endothelial cells</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Less than 1/3 of vein in cross section</td>
<td>1</td>
</tr>
<tr>
<td>1/3 to 2/3 of vein in cross section</td>
<td>2</td>
</tr>
<tr>
<td>More than 2/3 of vein in cross section</td>
<td>3</td>
</tr>
<tr>
<td>Inflammatory cell infiltration</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Few inflammatory cells in venous wall or perivascular tissue</td>
<td>1</td>
</tr>
<tr>
<td>Many inflammatory cells in venous wall or perivascular tissue</td>
<td>2</td>
</tr>
<tr>
<td>More diffuse and denser inflammatory cells in perivascular tissue</td>
<td>3</td>
</tr>
<tr>
<td>Edema</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Localized in perivascular tissue</td>
<td>1</td>
</tr>
<tr>
<td>More diffuse edema</td>
<td>2</td>
</tr>
<tr>
<td>Edema throughout the whole area</td>
<td>3</td>
</tr>
<tr>
<td>Thrombus</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Less than 1/3 of vein in cross section</td>
<td>1</td>
</tr>
<tr>
<td>1/3 to 2/3 of vein in cross section</td>
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</tbody>
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Investigations were limited to morphological observations.
AIM

To establish an animal model of infiltration induced by a hyperosmotic solution, a rabbit ear vein was administered with such a solution and observed specifically using immunostaining method.
METHOD

・Male Japanese white rabbit weighing from 2.5 to 3.5 kg was used.

・This study was approved by our Institutional Committee on the care and use of laboratory animals.

・Our facility (TERUMO corporation) has full accreditation by AAALAC International.
METHOD

Hyperosmotic solution was administered via the rabbit’s left ear vein and normal saline was infused via the rabbit’s right ear vein using PIVCs (24G).

Glucose: 36%
Osmolality rate: 2250 mOsm/L

The total infusion duration was 1 hr; infusion comprised 10 cyclic infusions with 1-min infusion each, and the solution in the vessel was clipped by clamps for 5 mins.
METHOD

• After administering the solutions, ear vein tissues were sampled and fixed in 10% neutral buffered formalin.

• Cross-sections of the ear vein tissues, one from a 30mm region in front of catheter tip were trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (HE) and immunostaining with CD31 and α-SMA antibody.

• Infiltration was defined as the presence of subcutaneous edema.
RESULTS (HE)

Normal saline (right ear vein)

Hyperosmotic solution (left ear vein)

vein

cartilage

edema
RESULTS (HE)

Hyperosmotic solution (left ear vein)

Some inflammatory cells (arrows) were observed in the venous wall.
RESULTS (CD31)

Normal saline (right ear vein)

Hyperosmotic solution (left ear vein)
RESULTS (NORMAL SALINE)

No damage to vascular endothelial cells (intact)
RESULTS (HYPERTONIC)

Loss of vascular endothelial cells caused by hyperosmotic solution
RESULTS (SMA)

Normal saline (right ear vein)
Hyperosmotic solution (left ear vein)

No damage to vascular smooth muscle infused by both normal saline and hyperosmotic solution
DISCUSSION

- According to the HE stained images, subcutaneous edema was observed in the tissue infused by hyperosmotic solution.

- There was no damage to vascular smooth muscle by hyperosmotic solution using α-SMA antibody.

- On the other hand, the vein infused by hyperosmotic solution showed loss of vascular endothelial cells using CD31 antibody.

This was the first study to show that infiltration (edema) was due to the loss of endothelial cells, not vascular smooth muscle, in veins infused by hyperosmotic solution.
FUTURE PLAN

The flow of the lower arm veins: 20 - 40 mL/min
The vessel flow of the upper arm: 100 - 150 mL/min

(Bard Access Systems. 2002)

The increased blood flow can dilute a drug’s osmolarity, reducing the risk of infiltration.

Future studies should compare vessel damage between different blood-flow-veins using this animal model, in order to implement these results into human.

Small vein (20-40 ml/min) VS. Large vein (100-150 ml/min)
Certified vascular nurses are not in Japan. Physicians are responsible of all VADs. Since 2002, Japanese nurses have been able to implement PIVC.
Our research group will suggest safe administration routes through mechanism based studies.
Conclusion

- Hyperosmotic solutions can lead to edema, defined as infiltration due to the loss of endothelial cells.

- This model can be useful in establishing safe administration routes and adequate PPN osmolality.

Limitation

- It is still unclear whether the administered solution leaked from the vein, or whether tissue fluid increased in surrounding subcutaneous tissue due to inflammation reaction.