



HYDROGEN PEROXIDE TRANSFER IN MEMBRANE OXYGENATORS

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M I C H E N E R . C A

Disclosure

History

• Womehulledcthlosisurgeobfillaliduarehthocxeate(Neshfyoirs in heater cooler units (HCU)



Concerns

- Does Hydrogen Peroxide diffuse into the patient's blood stream with plastic heat exchangers?
 - Should we be concerned?
- May other substances transfer across the heat exchanger?
 Methylene blue.
- Are all heat exchanger membranes the same?



Hydrogen Peroxide (H2O2)

- Initially believed to be a harmful byproduct of oxidative metabolism, H2O2 is now recognized to play key roles in intracellular signaling in normal physiology (Antunes and Brito, 2017).
- However, variations in H2O2 levels can induce pathological stress and result in deleterious effects.
 - H2O2 has also been implicated in myocardial ischemia reperfusion injury following myocardial infarction by activation subsequent inflammation and thereby causing cardiac cell injury and apoptosis (Wang, et al 2016)
- Very little is actually known about direct hydrogen peroxide injection into the blood stream



What does the literature say?

- Researchers could find <u>no peer reviewed</u> material on this subject
- Look to each devices IFUs and recommendations
- Medtronic has done their own in house study to evaluate this problem
 - They decided to look at the Medtronic Fusion, Sorin Inspire and Maquet Quadrox
 - Each houses a unique type of plastic heat exchangers

Medtronic's Research



No Migration is defined as being below the detectible limits of the test equipment (0.2 mg/L) as measured in a clinically relevant test setup

Decreases prime volumeEnables device incineration



Sorin's Inspire



- Liva Nova recommends the use of H2O2 with their 3T heater cooler units
- Liva Nova also acknowledges H2O2 may travel through the Inspire's heat exchanger membrane into the patient's blood.
- "For patients exposed over the duration of a CPB procedure (typically 6 hours or less), allowable limits were determined for the general population...For Inspire, our toxicological assessment has demonstrated that use of the 3T System devices for durations of six hours or less remains within allowable limits for patients with greater susceptibility to hydrogen peroxide. Allowable limits are lower for patients with increased H2O2 sensitivity. "

H2O2 Susceptibility

- Vitamin E deficiency
- Heritable deficiencies of the enzymes responsible for breakdown of H2O2
- Certain types of hemolytic anemia
- "However, this is not intended to be a complete list of all conditions that could impart greater H2O2 susceptibility"

Maquet - Quadrox



Additional testing has been performed to determine the diffusion rate of hydrogen peroxide through Maquet oxygenator heat exchangers after the release of the August 19, 2015 letter. These test results indicate that hydrogen peroxide diffuses through the TPU heat exchanger fiber for the period of 6 hours exceeds the computed daily allowable limits (AL):

- AL for adults (60 kg body weight): 12.60 mg/day
- AL for neonates (3 kg body weight): 0.63 mg/day
- The Quadrox IFU recommends to not use H2O2
- Maquet regonizes that H2O2 will readily diffuse through the heat exchanger bundle (along with Quadrox D)
- Recommend use of filtered water

Method Used to Evaluate The Membranes

- N of 3 for each of the following membranes:
 - Medtronic Fusion
 - Sorin Inspire 8
 - Quadrox-I



• Using 9 individual circuits, we primed a 3/8" loop with 1L of plasmalyte solution and recirculated through each oxygenator via a roller pump on a HL20 at 3 liters per min with a post membrane pressure of 200 mmHg.

Method Used to Evaluate The Membranes

- LivaNova 3T heater coolers were used with each of the membranes
 - Water was tested and maintained at 300 ppm H2O2 as per LivaNova Specification
 - Water was circulated at 37° C

Method Used to Evaluate The Membranes

- Samples were drawn off the oxygenator at:
 - 30 min
 - 1 hour
 - 2 hours
 - 4 hours



- Mquant Test strips used to test concentration of H2O2.
 - Both high range and low range strips were used
- 3T water supply was retested at 4 hours to ensure concentration of H2O2 at 300 ppm

Results





Results

- Were able to repeat the results produced by Medtronic
- No diffusion of H2O2 in the Fusion, however definite diffusion in the Quadrox and Inspire
- Quadrox did have the most diffusion over the test period
- Note*One unit from the Quadrox and Fusion did not transfer any H2O2 (water tested at completion and H2O2 concentration was confirmed)

Discussion

- Medtronic's Affinity Fusion had minimal transmission of hydrogen peroxide across its Polyethylene Terephthalate (PET) heat exchanger.
- Maquet's Quadrox and Liva Nova's Inspire both use a lower density polyurethane plastic for its heat exchange ability
- Comparing the permeability coefficients at 25 degrees of a gas like oxygen, it's observed that PET has a permeability coefficient of 0.035 compared to 2.2 of TPU

Discussion

- There is visible evidence of crossing over
- However, little is known on effects of H2O2 the patient
- Testing for allowable limits as performed by companies is not a peer reviewed process and not validated by clinicians
- Inconsistencies between lots
- Should we be cautious for ECMO with Quadrox-D
- What other substances may pass

Conclusion

• Changes at LHSC

Thanks to:





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Thank you for your attention!

Liva Nova – Legal.

- 3. Will the LivaNova's toxicological assessment be published or distributed to customers?
- The toxicological assessment is part of our Design History File which contains proprietary information related to our design. We are in a regulated industry where products are cleared or approved by Competent Authorities and/or Notified Bodies considering the results of our Verification and Validation activities (V&V). We do not provide the results of the V&V to customers who purchase our products to guarantee that our products are safe and effective but they can rely on our final product certification (CE mark, 510k approvals, ... other local approvals) to get this insurance.

Where Liva Nova Did tests

- Which laboratory conducted LivaNova's toxicological assessment?
- The toxicological assessment from which LivaNova determined the Allowable Limits for presence of hydrogen peroxide in the patient blood was conducted by IASON Consulting, a specialized laboratory located in Germany (Muehlenstrasse 26A D – 52382 Niederzier / Germany)