A Totally Recombinant Factor XIII-Supplemented Fibrin Sealant

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Disclosure/Conflicts:
None
Introduction

• Available fibrin sealants are plasma-derived (pd-FS)
• pd-FS contain fibrinogen + thrombin
• pd-FS does not much Factor XIII
• Some limitations of pd-FS: abundance & cost
Human Recombinant Fibrin Sealant (r-FS)

- rHu-Fibrinogen secreted in milk of transgenic cows
- rHu-thrombin available commercially (Recothrom®)
- rHu-Factor XIII made in yeast (*Pichia pastoris*)
- Factor concentration in r-FS optimized with TEG
TEG: effect of Factor XIII

Figure 3.11. Analysis of the effect of rFXIII on clot strength by thromboelastography. TEG monitored the change in clot strength over time of recombinant fibrinogen (8.56 mg/ml) activated by recombinant thrombin (52.8 U/ml) with (blue) and without (red) rFXIII (0.35 mg/ml). Data are expressed as mean +/- standard deviation.
TEG: r-FS vs. normal human blood (NHB)
Figure 4.10. Thromboelastographic properties of the optimized tri-component rLFS and a pdLFS (Tisseel®). Clots consisting of 15 mg/ml rFI, 0.59 mg/ml (4.095 U/ml) rFXIIIa and 0.33 mg/ml (176.7 U/ml) rFIIa (FXIIIa/FI = 0.16, FIIa/FI = 0.18) (blue) have faster clot kinetics and equivalent maximal clot strengths as a pdLFS (Tisseel®) as prepared by its manufacturer’s instructions (red). Tisseel contains 33.5 to 53 mg/ml pdFI and 200 to 312.5 U/ml pdFIIa. Data were expressed as mean +/- standard deviation.
Hepatic wedge excision model (domestic swine)

- Constant base dimension (1 cm)
- Incremental increase in depth dimension (0.5 to 3.0 cm)
- Six wedge excisions per series
- Two series per swine (i.e., two lobar edges)
- N = 6 swine per group (r-FS vs. pd-FS)
Fibrin sealant delivery

Tisseel® Duploject® syringe
(Baxter Biosurgery)
Fibrin sealant delivery

Tisseel® Duploject® syringe
(Baxter Biosurgery)

System without a common mixing channel
Hepatic wedge excision model

pretreatment

post-treatment
red: human FI
brown: porcine FI

IHC
Results

Hemostasis Score definitions:
0 = failure/minimal effect
1 = steady bleeding
2 = oozing
3 = hemostatic

Each bar = mean ± sd of 10-12 excisions
Vital signs during a typical testing period

*Euthanasia

Serum TEG data also was unchanged before, during, and after procedure (DNS)
Aerosol delivery of r-FS
Aerosol delivery of r-FS

Go to video: "Aerosol Delivery of r-FS"
Conclusions

• r-FS had equivalent or better hemostatic efficacy compared to pd-FS, despite the [FI] in r-FS being about one-third of that in the pd-FS.

• The r-FS performance may be due to the TEG-optimized proportions of FI, FII, and FXIII.
Future

- r-FS production is scalable
- 100 transgenic cows = ~1 metric ton of FI per year
- Cost vs. pd-FS could be much less
- Production of other human recombinant proteins?