

Compatibility of Oxytocin and Tranexamic Acid Injection Products

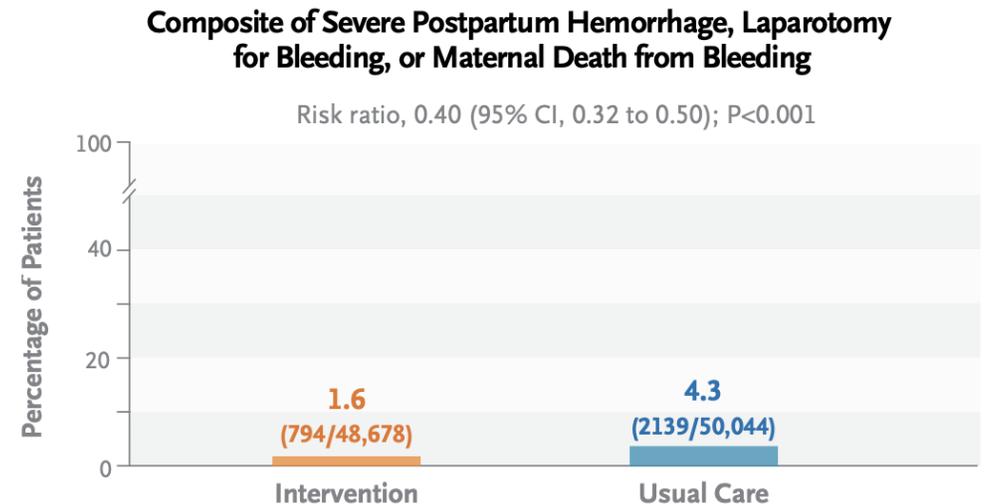
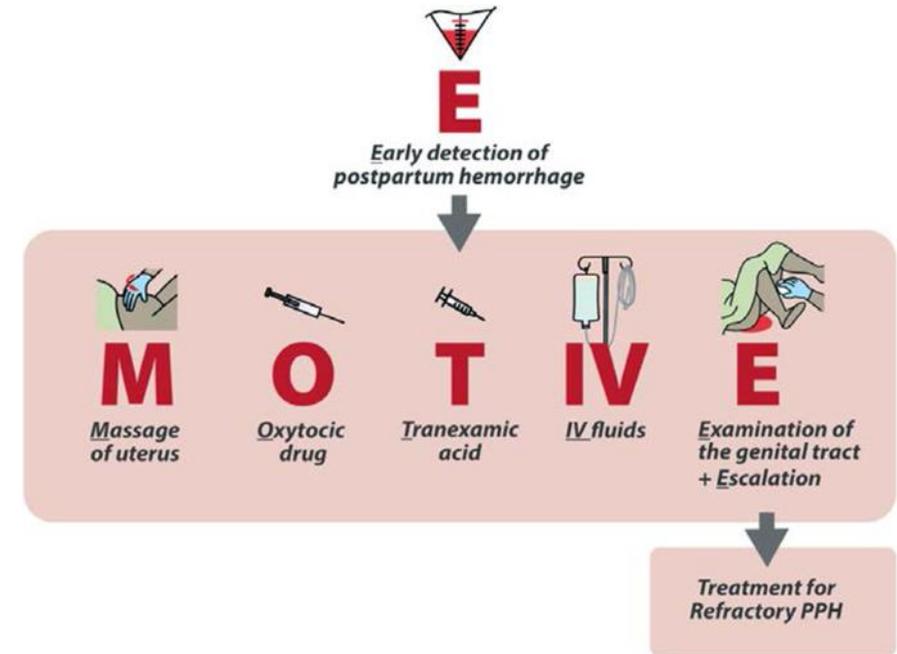
Pete Lambert - Director, Monash Quality of Medicines Initiative, Monash University
Maternal Health Supplies Caucus

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E-MOTIVE Protocol

Early Response for Treatment of PPH

- Comprises four key elements:
 - Uterine massage
 - Administration of:
 - Oxytocin (OXY) injection
 - Tranexamic acid (TXA) injection
 - Intravenous fluids
- Assessed in large scale clinical trial
 - ~210,132 vaginal births in Nigeria, Tanzania, Kenya and South Africa
 - 60% reduction in sPPH, laparotomy or maternal death from bleeding
- Quality assessment of OXY and TXA products conducted prior to/during early stages of study



E-MOTIVE Protocol

Quality of PPH Products Used in the Study

OXY Quality Results

- 17 products assessed
- Drug content
 - 10/17 products passed drug content specification (90-110% of labelled content)
 - 7/17 products failed drug content specification (69.3% and 89.2%)
- Related Substances/Impurities
 - 10/17 products passed related substances/impurity specification
 - 7/17 products failed related substances/impurity specification (nmt one impurity >2%, no impurity >5%)

TXA Quality Results

- 18 products assessed
- Drug content
 - 17/18 products passed drug content specification (95-105% of labelled content)
 - One product showed minor out-of-specification result in 3 of 4 ampoules tested (93.6-94.6%)
 - 11/18 products passed the related substances /impurities specification (no impurity >0.2%)
 - 6/18 products failed specification with related substances/impurity content between 0.2-2%
 - One product exhibited gross failure with related substances/ impurities of as high as 250%

➤ **Clinical sites were notified to exclude poor quality products from the E-MOTIVE study**

E-MOTIVE Protocol

Quality of PPH Products Used in the Study

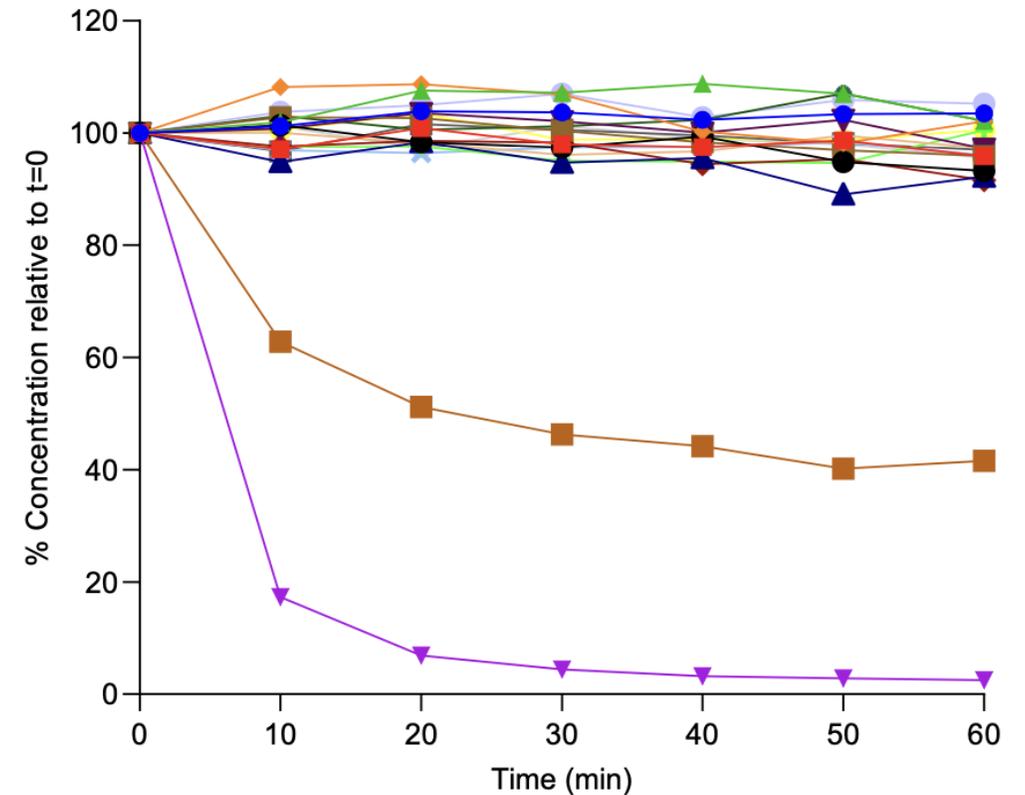
Summary

- Both OXY and TXA products showed quality issues
- First study indicating quality issues with TXA injection products
- Oxytocin products demonstrated issues of drug content and impurities
 - Oxytocin impurities included known degradation products and other impurities indicating issues of both storage and manufacturing quality
- TXA quality issues largely limited to related substances/impurities most likely associated with manufacturing

E-MOTIVE Protocol

Can OXY and TXA be mixed for administration with IV fluids

- Question from clinical sites:
“To simplify administration, can OXY and TXA be mixed and co-administered with the IV fluids?”
- No studies previously conducted to investigate this question
- Screen conducted of 18 TXA products combined with a good quality (not SRA-approved or quality assured) OXY product.
 - Small volume study (~1mL) due to limited availability of supplies
 - Concentrations matched those that would be used with a 200mL IV infusion
 - 0.9%w/v saline used as diluent
 - Compatibility assessed over 1 hour



E-MOTIVE Protocol

Can OXY and TXA be mixed for administration with IV fluids

Follow up Investigations:

- OXY and TXA drug substances (i.e. when not formulated as injection products) do not interact with each other therefore....
 - ... the loss of oxytocin is likely due to an interaction with a non-drug component/impurity within these TXA formulations.
 - Both TXA formulations contain significant impurities not present in the SRA-approved innovator product (Cyklokapron®) however:
 - Not all of these impurities can be detected using the pharmacopoeial methods
 - A number of the other TXA products contain high levels of impurities and do not interact with OXY
 - It is not yet clear which impurity is responsible for the interaction with OXY (investigations ongoing)
- OXY and TXA injection products should **NOT** be mixed for co-administration

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