Challenges around the introduction of a new product for Intra Uterine Transfusion

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Introduction

- Hemolytic disease of the fetus or newborn (HDFN)
  - Immune: Maternal IgG antibodies → hemolysis, anemia
  - Non-immune: infections, fetomaternal hemorraghe
- Without treatment → cardiac arrest, hydrops fetalis, mortality
- Treatment → Intra Uterine Transfusion (IUT), 25-50 patients per year

Introduction

- Number of IUT treatments: 1-8, median 3
- Current routine:
  - RCC (160-240 mL) for IUT prepared from stored leukoreduced RCC <72 uur,
  - blood group O, Rh D neg, K-neg,
  - CMV neg, Parvo B-19 safe
  - best match for maternal antibodies and Rh (Cc, Ee), Jk, Fy, S

Introduction

- IUT treatment results in > 90% perinatal survival but:

- some disadvantages:
  1) In > 20% additional maternal antibody formation.

  2) Donor exposure 1-8

  3) Substantial wastage: volume needed 2 – 142 mL, median 56 mL

Aim of the project

- To improve matching and to minimize donor exposure for mother and child, treated with IUT
  - Development of a new blood bank process starting with **matching from donor pool instead of products on the shelf**
  - Design of a new RCC preparation method for IUT using small volume whole blood donations: **one donor can donate repeatedly for same recipient**

Part I: donor management

Q: Will donors volunteer to donate small volumes WB for several times after a call?

A: Experience with HLA/HPA typed platelet apheresis, should be no problem; cohort should be formed with informed consent

Q: Are there any disadvantages for the donor to donate several times 100 or 200 mL of WB instead of 500 mL ?

A: No medical complications to be expected

Q: Follow up of donors who participate in the new procedure?

A: Precautionary: monitor Hb and satisfaction

Part II: QAR

Q: What has to be done to change donation interval, procedures (SOP), guidelines, blood bank information system, etc. ?

A: Donation of 60 mL/week allowed instead of blockade for 56 days after donation of 500 mL

- > 90% of treatments theoretically 1 donor (1-5 donations in 2 months)
- > 90% of treatments with 100 or 200 mL donations

A: ePrognesa to be adapted to allow 100 and 200 mL donations

A: SOP's to be written; procedures to be validated and trained

Part III: Product development

Q: How to prepare an RCC for IUT from 100 or 200 mL WB

A: Leukoreduction as whole blood after dilution with 0.9% NaCl

Hard spin to remove plasma

Wash with saline to reduce anti A/B

Q: How to collect 100 or 200 mL WB

A: reduce volume of anticoagulant in standard collection system

Q: how about *in vitro* quality?

Experiments with aliquots of 500 mL WB

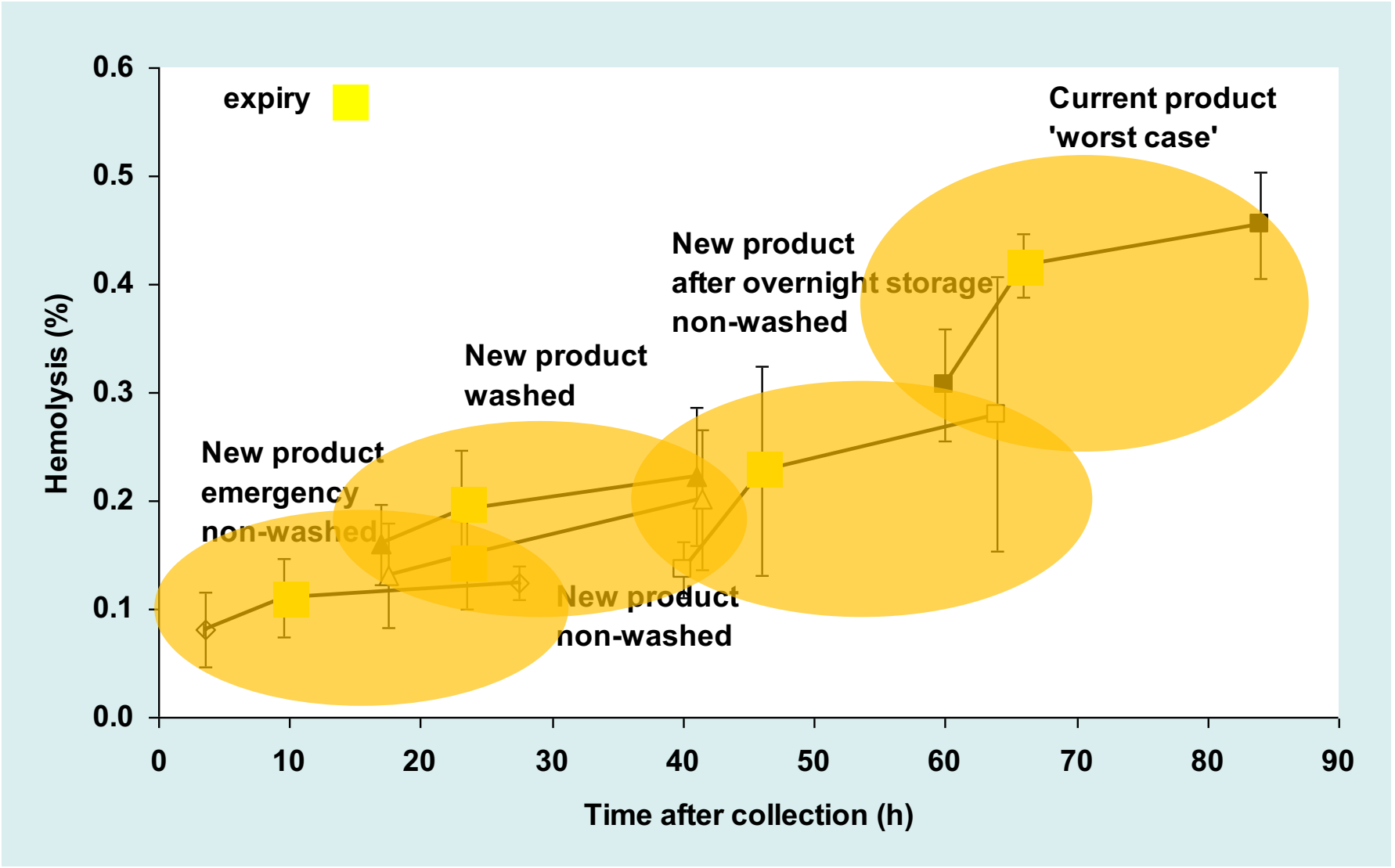
- *In vitro* quality after (routine) overnight storage of small WB volume ? → acceptable and comparable with current product
- *In vitro* quality after only 2 h cooling/storage of small WB volume (emergency procedure) ?
  → no differences
- *In vitro* quality in case of delayed transfusion
  (D0 collection; D1 preparation; D2 irradiation) ?
  → slightly more hemolysis and K^+ leakage
- Effect of wash procedure on anti-A / -B titers ?
  → substantial effect; after washing ≤ 1:2

RCCs from 4 small WB donations

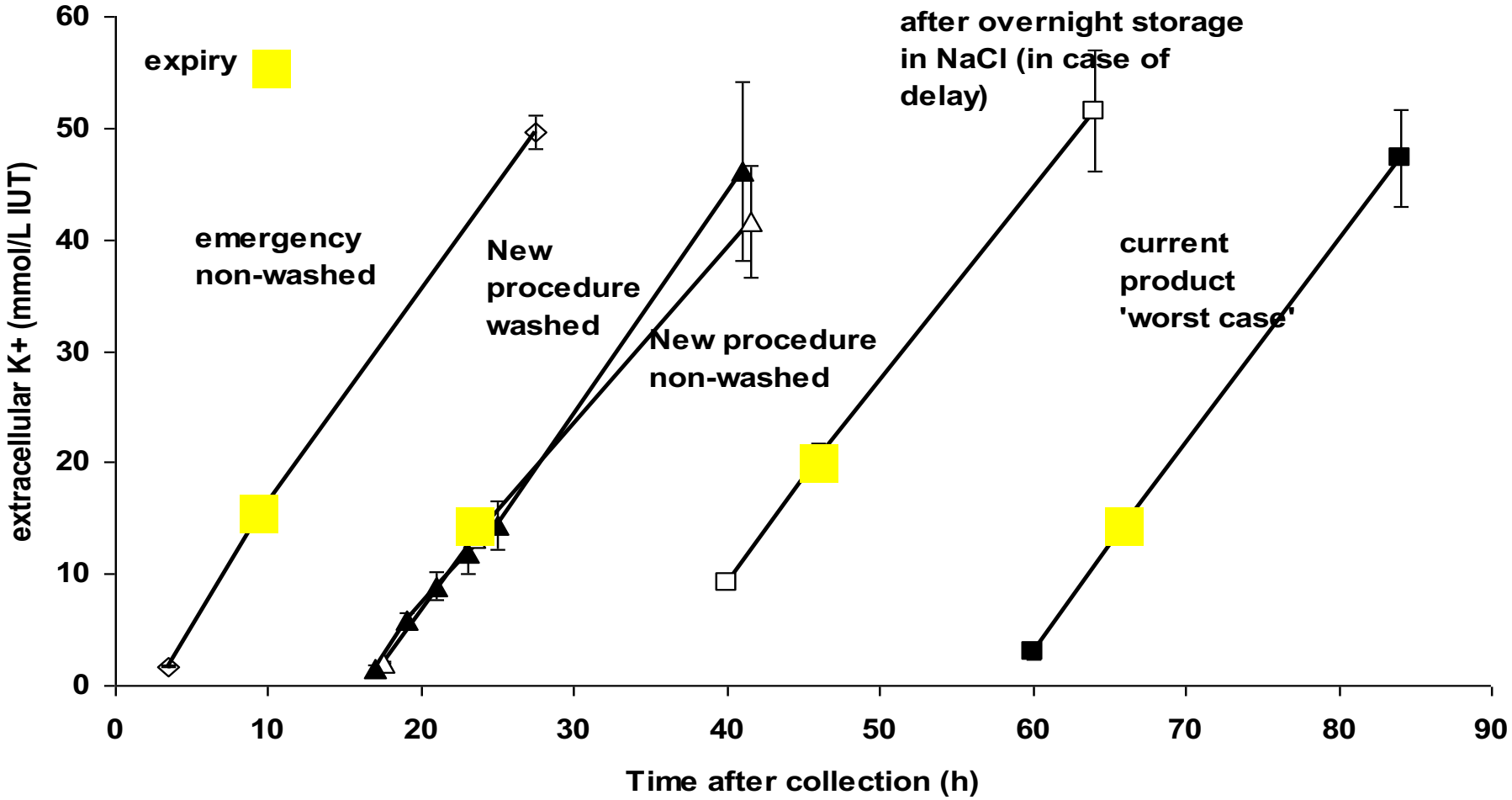
Unit nr.	1; 2	3; 4
Set WB volume, mL	110	210
Wash procedure	yes	no
Whole Blood		
Volume, incl CPD, mL	148; 116	226; 226
Titer anti-A	NR; 512	NR; 512
Titer anti-B	128; 512	128; 256
Red cell concentrate		
Volume, mL	54; 49	79; 93
Hematocrit, L/L	0.85; 0.85	0.87; 0.87
Hemoglobin, g	14; 13	21; 24
RBC recovery, %	84; 85	91; 92
Leukocytes, $x10^6$	<0.01; <0.01	0.01; 0.01
Titer anti-A	NR; neg	NR; 256
Titer anti-B	neg; neg	16; 32

NR: not relevant

Hemolysis 6 and 24 h after irradiation



Extracellular K^+ 6 and 24 h after irradiation



Conclusions Design Phase

- RC of 100
  or 2 *vitro*
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- Re bank
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- A w ve
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Go for Implementation with Project Team

Implementation Challenges

- How to organize; discussions with treating physicians about ordering on time

  Monday/Tuesday: ordering and donor matching, mini-donation system preparation (adjustment anti-coagulant volume) and transport to collection site

  Wednesday: collection of mini-donation and transport to Amsterdam

  Thursday: production of IUT-RCC, irradiation, transport and IUT treatment

- Theoretically possible to improve prediction for IUT need and already perform blood group typing mother, but practical problems in hospital

- Difficult to change routine
- Urgent orders very difficult to realize on time (mainly donor/donation part)

Implementation Challenges

- Complicated process with lots of deviations from SOP's in use and manual checks
- Two products needed: 100 mL and 200 mL donations
- Complicated logistics (adaptation blood bag system, transport, donor selection; special program collection scale)
- Existing method still needed for urgent orders

- Training needed for many teams (collection everywhere)
- Limited experience (60 – 100 per year)

- Questionable if quality can be warranted, high risk for errors
- In case of error: old method, benefit lost

Implementation Challenges: Benefit?

- Since development started consolidation: larger stock of units <72 h old and better defined (typing)
- Over the years:
  - Improved matching; 84 vs 71 % of units matched; only matched: 60% vs 43%
  - Limited benefit expected from new product, because non-matching mainly in case of urgent IUT (7 out of 9 unmatched per year)
  - Reduction in percentage additional maternal antibody formation after IUT from 25% to 14 %; *Schonewille et al. Transfusion 2015*
  - Questionable if further reduction can be reached
  - Part of antibody formation by fetus

Final Decision

- New product will **not** be implemented
  - Low theoretical benefit, high theoretical risk
  - High costs

- In cooperation with physicians:
  - Attention for prediction of probable need for IUT
  - Further reduction of urgent orders to prevent mismatch
  - Extended antigen typing of the mother at the first visit

Lessons Learned

- Know exactly what your customers want
- Involve the whole chain in your project team
  - All aspects of the process to avoid late surprises
  - Team members responsible for acceptance in their teams
- Check if there are changes during the development
- Stay open for alternatives
- Be flexible

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