Temperature-Sensitive Indicators for Monitoring RBC Concentrates Out of Controlled Temperature Storage

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ABSTRACT

Objectives: *The 30-minute rule for RBC concentrates out of controlled temperature storage does not take into account multiple parameters that influence warming of RBC concentrates. This study evaluated two temperature-sensitive indicators (TIs) for monitoring RBC concentrates during transport.*

Methods: *TI labels (Check-Spot [Harald H. Temmel KG, Gleisdorf, Austria] and Thermoindikator V4 [BASF, Basel, Switzerland]) were attached to RBC concentrates prior to delivery. Duration of transport, ambient temperatures, and label results (valid vs expired) were recorded. We evaluated the proportion of labels discrepant to the 30-minute rule overall and among deliveries 30 minutes or less and more than 30 minutes and compared the rates of valid and expired readings between both TIs.*

Results: *In total, 201 RBC concentrate deliveries (86.6%) lasted 30 minutes or less, and 31 (13.4%) were more than 30 minutes. Forty-six (19.8%) Check-Spot and 37 (15.9%) Thermoindikator V4 results were discrepant to the 30-minute rule. Sixteen (51.6%) and 27 (87.1%) RBC concentrate deliveries more than 30 minutes displayed valid label readings with Check-Spot and Thermoindikator V4, respectively. Rates of expired labels among deliveries 30 minutes or less and valid labels among deliveries more than 30 minutes differed significantly between TIs ($P < .01$).*

Conclusions: *TIs identified a considerable number of RBC concentrates whose temperatures may not be adequately reflected by the 30-minute rule. Variability of readings between TIs stresses the necessity of validation prior to implementation.*

Specifications defined by the regulating authorities set standards for storage and transport of RBC concentrates. RBC concentrates should be stored at 1°C to 6°C (United States) or 2°C to 6°C (Europe); during transport, temperature should not exceed 10°C.[1-3]

When RBC concentrates are removed from controlled temperature environments (eg, during in-hospital transport), the 30-minute rule is applied. It states that RBC concentrates left out of controlled temperature storage for more than 30 minutes should not be returned to storage for reissue and consequently be discarded if there is no prospect of imminent transfusion.[1] The 30-minute rule is based on the observation that the upper limit of 10°C, which is applied for transport of blood products, can be reached in 30 minutes if RBC concentrates taken from refrigerated storage are left at ambient temperature.[4]

However, the 30-minute rule as a time-based surrogate for temperature monitoring of RBC concentrates does not take into account a multitude of parameters besides time that influence individual RBC concentrate warming: volume and width of the RBC concentrate storage bag, thermal isolation (eg, air cushion envelopes), sample handling, and exact storage and ambient temperatures the RBC concentrates are exposed to, including variations in air conditioning and solar radiation.[5-8] In addition, the dynamics of RBC concentrate warming also depend on the number of units packed together.[9] Thus, time-based rules potentially contribute to unnecessary wastage, since RBC concentrates will be discarded even if core temperature is still within acceptable limits, and may be detrimental for patient safety, since RBC concentrates with elevated core temperatures may remain undetected. Temperature-sensitive indicators (TIs) can circumvent these

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issues, since they monitor temperatures of individual RBC concentrates.

The present study evaluated two different TIs, Check-Spot (Harald H. Temmel KG, Gleisdorf, Austria) and Thermoindikator V4 (BASF, Basel, Switzerland), for monitoring RBC concentrate temperatures during delivery by a pneumatic tube system in a university hospital setting. We monitored transport times and ambient temperatures and compared the labels' results (valid vs expired) with the 30-minute rule.

Materials and Methods

Study Design

This was a prospective single-center comparative study. The protocol was approved by the local ethics committee.

Leukoreduced RBC concentrates (275 ± 75 mL) in saline-adenine-glucose-mannitol or phosphate-adenine-glucose-guanosine-saline-mannitol were obtained from regular blood donors, processed, and tested according to Swiss national guidelines and stored at controlled temperatures of 4 ± 2°C at the Blood Transfusion Center (BTC). In general, RBC concentrates are transported from the BTC to the wards of the University Hospital Basel (USB) via a pneumatic tube system. Each pneumatic tube container holds a single RBC concentrate; each RBC concentrate is placed into an additional plastic tube prior to placement in the pneumatic tube container. For study purposes, only RBC concentrates ordered for patients on the hematologic ward of the USB were eligible, to limit the number of nursing staff to be trained in indicator interpretation. Both TIs were placed side by side right above the lower third of each RBC concentrate bag, with special focus on comparable positioning by specially trained BTC laboratory technicians. Labeling took place immediately prior to removal from refrigeration for preparation for pneumatic tube transport. The time of removal was recorded at the BTC but was not disclosed to the receiving staff at the USB.

Description of TIs

Both labels are displayed in **Figure 1**. Check-Spot is a self-adhesive label with an integrated temperature indicator. It is activated when fixed on the surface of the RBC concentrate through a manufacturer-supplied mechanical device (Spot-Gun; Harald H. Temmel KG). According to the manufacturer, the indicator has been calibrated to begin to change from white to finally dark red when the blood bag core temperature reaches 9.6°C. At 10.4°C, color change ceases and is irreversible; accuracy is ± 0.5°C. Verification studies, including lot-to-lot analysis, have been published previously.[10]

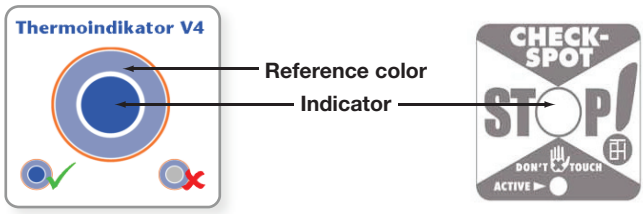

Figure 1 Thermoindikator V4 and Check-Spot (reprinted with permission).

Thermoindikator V4 is a prototype of a self-adhesive label that contains photochromic pigments that fade depending on both time and temperature. The labels' pigments are activated by a small UV charging device. After application to the blood bag, a self-adhesive filter label prevents accidental reactivation. The label color continuously fades over time, the speed of fading being dependent on the surrounding temperature. A reference color has been calibrated and validated at our institution to reflect RBC concentrate temperature after storage at 22°C for 30 minutes. The end point is indicated when the label color has reached the color of the surrounding reference.

Data Acquisition, Study End Points, and Statistical Analysis

Each RBC concentrate delivered to the USB was accompanied by a standardized report form to record reception time, label reading ("valid" vs "expired"), and functional criteria (adhesion of label to the RBC concentrate, ambiguity of label reading) of each label by the nursing staff. In addition, time of arrival of each RBC concentrate at the pneumatic tube exit was obtained from the pneumatic tube transport surveillance system. Based on the recordings at the BTC and USB and by the surveillance system, transit time (interval BTC—pneumatic tube exit) and delivery time (interval BTC—reception by nursing staff) were calculated. On days of delivery of RBC concentrates, ambient temperatures at the BTC and intermittently at the USB were recorded with conventional thermometers (Koch Thermometer GmbH, Kuelsheim, Germany). Minimum and maximum temperatures within the pneumatic tube system were intermittently recorded on delivery days by placing a temperature logger (Koch Thermometer GmbH; recording minimum and maximum temperature at 10-second intervals) into a pneumatic tube container and sending it from the BTC to USB or vice versa.

Outcome parameters included the proportion of discrepant readings to the 30-minute rule for each TI (ie, TI indicating RBC concentrate is "valid" with a delivery time >30 minutes or TI indicating RBC concentrate is "expired" with a delivery time ≤30 minutes) overall and among deliveries 30 minutes or less and more than 30 minutes. We compared

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Table 1
Transport Times and Temperatures During Transport of RBC Concentrates via Pneumatic Tube System

Characteristic	Median	Minimum-Maximum	95% Range
Transit time, min:s (n = 213)	4:34	2:05-24:16	2:32-14:09
Delivery time, min:s (n = 232)	15:00	3:00-199:00	4:46-69:27
Temperature BTC, °C (n = 232)	24.3	21.3-26.5	NC
Temperature USB, °C (n = 27)	25.0	24.0-26.0	NC
Temperature minimum, pneumatic tube, °C (n = 27)	22.5	17.0-24.5	NC
Temperature maximum, pneumatic tube, °C (n = 27)	27.0	24.4-29.5	NC

BTC, Blood Transfusion Center; NC, not calculated; USB, University Hospital Basel.

the rates of valid and expired labels between Check-Spot and Thermoindikator V4 and evaluated the functional criteria for each label as recorded on the standardized report form.

We used Microsoft Excel (Microsoft Corporation, Redmond, WA) for data entry and R (R Foundation for Statistical Computing, Austria, Vienna) for statistical analyses. Data were compared by the χ^2 test or Wilcoxon rank-sum test, where appropriate. A P value less than .05 was considered statistically significant.

Table 2
Delivery Times and Results of Check-Spot and Thermoindikator V4[a]

	Check-Spot, No. (%)		Thermoindikator V4, No. (%)	
Delivery Time	Valid	Expired	Valid	Expired
≤30 min (n = 201)	171 (85.1)	30 (14.9)	191 (95.0)	10 (5.0)
>30 min (n = 31)	16 (51.6)	15 (48.4)	27 (87.1)	4 (12.9)

[a] $P < .01$ for comparisons of Check-Spot vs Thermoindikator V4.

Results

Between October 2010 and March 2011, a total of 258 RBC concentrates delivered to the USB were labeled; for 11 RBC concentrates, the report form was missing, and 15 had incomplete report forms with missing time of reception at the USB or lack of TI status. Therefore, 232 RBC concentrates were available for evaluation.

Table 1 gives the transit times (interval BTC—pneumatic tube exit) and delivery times (interval BTC—reception by nursing staff) as well as ambient temperatures at the BTC and USB and temperature recordings within the pneumatic tube system. The median delay from RBC concentrate arrival at the pneumatic tube exit until reception by the nursing staff was 8:22 minutes (95% range, 1:24-56:52 minutes). When comparing transit and delivery times of RBC concentrates delivered on weekdays at daytime (Monday-Friday, 8:00 AM to 5:00 PM) with RBC concentrates delivered on weekdays at nighttime (Monday-Friday, 5:00 PM to 8:00 AM) or weekends (Saturday-Sunday), the median of difference for transit time was 1:00 minute (95% confidence interval [CI], 0:01-2:00) ($P < .001$) in favor of nighttime/weekends, in line with the generally decreased utilization of the pneumatic tube system during these times. For delivery time, the median of difference was 19:00 minutes (95% CI, 12:00-25:00) ($P < .001$) in favor of weekdays at daytime, reflecting the higher number of nursing staff present during regular hours.

While ambient temperatures at the USB showed only minimal variation, temperature at the BTC varied between 21.3°C and 26.5°C. Within the pneumatic tube system overall, temperature ranged from 17.0°C to 29.5°C. For individual measurements, the median difference between minimum and maximum temperature within the pneumatic tube system was 4.5°C (range, 0.7°C-9.5°C).

In total, 201 (86.6%) RBC concentrates had a delivery time of 30 minutes or less; 31 (13.4%) RBC concentrate deliveries lasted more than 30 minutes. **Table 2** gives the corresponding TI readings. Overall, Check-Spot labels were valid on 187 (80.6%) and expired on 45 (19.4%) RBC concentrates; for Thermoindikator V4, the corresponding numbers were 218 (94.0%) and 14 (6.0%). Forty-six (19.8%) Check-Spot and 37 (15.9%) Thermoindikator V4 label readings were discrepant with regard to the 30-minute rule ($P = .33$). The rate of expired labels among deliveries 30 minutes or less was significantly different between Check-Spot and Thermoindikator V4 (difference between rates, 10.0%; 95% CI, 3.7-16.2; $P < .01$). A significant difference between the two labels was also found for the rate of valid labels among deliveries more than 30 minutes (difference between rates, 35.5%; 95% CI, 11.1-59.9; $P < .01$). Concordance of readings between Check-Spot and Thermoindikator V4 is displayed in **Table 3**. For 193 (83.2%) RBC concentrates, results of both TIs were identical, with 28 (12.1%) discrepant results for RBC concentrates delivered within 30 minutes or less and 11 (4.7%) discrepant readings for RBC concentrates delivered after 30 minutes. Thermoindikator V4 had few expired readings overall. Only four discrepant readings between TIs were due to expired Thermoindikator V4 (with valid Check-Spot); in the 35 remaining cases, Check-Spot was expired (with valid Thermoindikator V4).

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Table 3
Concordance of Label Results Between Check-Spot and Thermoindikator V4

Delivery Time	Check-Spot Valid, No. (%)	Check-Spot Expired, No. (%)
≤30 min (n = 201)		
Thermoindikator V4 valid	167 (83.1)	24 (11.9)
Thermoindikator V4 expired	4 (2.0)	6 (3.0)
>30 min (n = 31)		
Thermoindikator V4 valid	16 (51.6)	11 (35.5)
Thermoindikator V4 expired	0	4 (12.9)

The labels' functional criteria according to the nursing staff were good: adhesion to RBC concentrates was no issue for both labels; in five (2.1%) and eight (3.4%) instances, label interpretation was judged ambiguous for Check-Spot and Thermoindikator V4, respectively.

Discussion

RBC concentrate warming is influenced by a multitude of factors. Besides the duration and degree of "uncontrolled" temperature exposure, it also depends on preexposure storage temperatures, RBC concentrate pouch width, and, to a lesser degree, RBC concentrate volume.[6] Further variables in RBC concentrate warming are occasional ventilation, air conditioning, solar radiation, sample handling, or the number of units involved.[7,9] Time-based rules can therefore only be an estimate of the individual warming process. With regard to the 30-minute rule, core temperature of RBC concentrates removed from refrigerated storage at 6°C will remain below 10°C during a 30-minute exposure only if ambient temperature does not exceed 20°C.[8] Consequently, time-based rules can contribute to unnecessary wastage and are potentially detrimental to patient safety. TIs can address these issues since they monitor temperatures of individual RBC concentrates. In our study, 19.8% of Check-Spot and 15.9% of Thermoindikator V4 readings were discrepant to the 30-minute rule. These rates suggest that a considerable number of individual RBC concentrate temperatures may not be adequately reflected by the 30-minute rule.

Our results also show that Check-Spot and Thermoindikator V4 differ significantly in their readings. TIs vary in their accuracy of reflecting core temperatures.[10] For Check-Spot, which is calibrated to a temperature limit of 10°C, the final color change occurs between 10°C and 11.9°C RBC concentrate core temperature.[10] However, Thermoindikator V4 has "only" been validated to reflect RBC concentrate temperature after storage at 22°C for 30 minutes (and not to reflect RBC concentrate core temperature at 10°C). This possibly accounts for the differences observed. Our results therefore stress the importance of proper validation of labels prior to implementation.

For routine use of TIs for monitoring RBC concentrate temperature, some general aspects need to be considered. First, TIs are designed to predict core temperatures from RBC concentrate surface temperature. However, surface and core temperature curves of RBC concentrates removed from refrigerated storage to ambient temperature differ markedly.[7] Prediction of RBC concentrate core temperature is also influenced by the gradient of storage to ambient temperature.[8] Since thermal insulation reduces temperature and time drifts between RBC concentrate surface and core temperatures during warming,[7] it can ensure validity of label readings with respect to representing RBC concentrate core temperature. In our study, insulation was achieved through placement of each individual RBC concentrate in an additional plastic tube within the pneumatic tube container. Besides ensuring the validity of our label readings with regard to core temperature, thermal insulation certainly also had a positive impact on the rate of valid label readings in our study. Second, TIs are only capable of monitoring RBC concentrate temperature at the location they are attached to. Therefore, positioning of TIs on the individual RBC concentrate can be critical. During warming, heat is transferred from higher to lower temperatures, defining the thermal RBC concentrate core as a position where temperature limits are exceeded the latest. Since duration of heat transfer critically depends on the distance heat must be transported,[6] the thermal RBC concentrate core is located at the point of the largest pouch width of the individual RBC concentrate. It is therefore reasonable to choose this location for TI placement. In our study, TIs were positioned right above the lower third of each RBC concentrate bag, which approximately corresponds to the area of the largest pouch width of RBC concentrates in a lying or upright position. It is important to note that transport by a pneumatic tube system caused repetitive agitation and mixing of RBC concentrates content. Therefore, the temperature gradient within each RBC concentrate during warming was less than in resting RBC concentrates, making placement of TIs exactly at the area of the largest pouch width less critical and imperative. The third aspect of TI application is related to the interpretation of color changes. Label readings and interpretations have to be simple and unambiguous; otherwise, they will contribute to unnecessary wastage.[11] Only a few cases of ambiguous label readings were reported in our study for either Check-Spot or Thermoindikator V4. However, variability in label reading and interpretation tends to be lower if labels apply definite (eg, white to red) instead of graded color changes.[11]

Recently, a number of studies have examined the impact of various scenarios of RBC concentrate exposures to temperatures ranging from 10°C to 30°C on RBC concentrate

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quality and bacterial growth.[12-17] As a result, some authors have been advocating that the duration of RBC concentrates to be allowed out of controlled temperature storage and still be eligible for return to storage for reissue should be extended from 30 to 60 minutes.[14,17,18] This would certainly lead to a reduction of RBC concentrate discard. In our study, the rate of expired RBC concentrates would have decreased from 13.4% (30-minute rule) to 3.9% (60-minute rule). However, the limitations of any time-based rule for ensuring RBC concentrate quality out of controlled temperature storage would still apply, and the number of RBC concentrates with expired core temperatures remaining undetected would most likely increase. TIs would therefore still be an adequate choice for ensuring quality and safety of RBC concentrates. In our view, if a consensus could be reached that the current 10°C temperature limit represented by the 30-minute rule could be raised, this should be done by establishing a new acceptable core temperature limit, since RBC concentrate core temperature is the key issue. This limit can serve as the basis for the recalibration of TIs and, if desired, establishment of a new time limit as second-choice surrogate. The latter could be defined with the help of existing heat transfer models[6,8] and the use of empirical data.

There are two major limitations to our study. First, we did not measure the temperature of RBC concentrates at the time of reception to validate TI readings. Since this study was performed in a clinical setting with RBC concentrates destined for patients, neither invasive measurement through probes (risk of bacterial contamination) nor thermography (delay of transfusion) to establish core temperature was feasible. The second limitation is that we do not report any numbers on actual wastage since all RBC concentrates in our study were transfused upon reception. The rate of RBC concentrates with delivery time more than 30 minutes or with expired TI is not equivalent to wastage since these RBC concentrates are suited for imminent transfusion. They may not, however, be returned to storage for reissue and should be discarded instead.[1] According to the annual UK Blood Stock Management Scheme report, wastage due to "being out of temperature control" accounted for up to 45% of total in-hospital RBC concentrate wastage.[19] Another study reported a rate of 71% of RBC concentrate in-date wastage due to violation of the 30-minute rule.[11]

Conclusions

Our study shows that TIs identified a considerable number of RBC concentrates whose temperatures may not be adequately reflected by the 30-minute rule. However, variability of readings between TIs stresses the importance of proper validation prior to implementation.

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