Real Time Monitoring of Erythrocytes With the QTA Tracer System At the Ryhov County Hospital Blood Center Resulted in Changed Routine

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Master Thesis in Medicine

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Abstract

Introduction About 500 000 blood units are collected from blood donors and used for the preparation of blood components for blood transfusion in Sweden every year. The shelf life of a red blood cell (RBC) unit in SAGM solution is 42 days within a controlled temperature environment of 2-6˚C. There is limited knowledge about how time and especially temperature affect blood units. However, even today´s blood units all over the world are transported to different health care sites without a guaranteed quality control of the required cold-chain.

Purpose The purpose of this thesis is to explore the actual temperature variation during internal storage and internal transports of blood units during its actual shelf life in its real environment.

Method At the Blood Center at Ryhov the QTA Tracer System® was used log the temperature and time. Tracers were attached to blood bags that then were stored at the internal refrigerators or transported between Jönköping and Värnamo.

The log-files were then analyzed with excel spreadsheet to identify individual blood bags, i.e. tracers, that were out of temperature range.

Conclusions The test showed that there were actual deviations from the standards in the physical environments surrounding the blood bags even though the procedures were followed. To all the blood bags that reached below 0°C a control of their level of hemolysis were performed. The fact that all of them had well below the stipulated 0.8% of hemolysis could raise the question of the 'zero-tolerance' to go below 0°C due to the risk of hemolysis.

The blood center made some minor changes to some of procedures to reduce the deviations. They also continuously monitor their blood bags to incremental develop their routines.

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1 Introduction

1.1 Background

Red blood cells (RBC) are an important ingredient in the modern emergency, transplantation, hematology and health care system. RBC in vivo is known to have a lifespan of approximately 120 days. RBCs for medical use are normally derived from whole blood donations and stored in a cold environment in an additive solution for approximately 42 days [1, 2].

Sweden are today self-sufficient of blood cells but the availability of RBC are however scarce. Almost 500 000 whole blood units are collected from blood donors and used for the preparation of blood components for blood transfusion and production of blood components in Sweden every year. This amount is still sufficient enough but there is a trend that the pool of donors is diminishing both nationally and internationally. This is due to the facts that lesser donors volunteer and through better planning, lesser elective surgeries and medical innovations that limit the bleeding during surgery [3-5].

The shelf life of a red blood cell RBC unit in a SAGM solution is 42 days within a controlled temperature environment of 2-6°C. The handling of blood bags, processing, storage and transport is regulated by different international, national and local standards [6-8].

There is limited knowledge about how time and especially temperature affect blood units. Reviews and articles publicized back since the fifties are not conclusive on the sensitiveness of blood bags [9]. According to Thomas et al. 'Red cells may be damaged to prolonged exposure to warm temperature, but repeated short-term exposure to +22C or -2C does not appear to affect the in vitro quality of RBC'[10]. This is in

line with the finding of Gulliksson et al. that argues 'that quality of RBCs after transient warming will be maintained at acceptable levels'[11]. They though argue that 'increased haemolysis was observed …during the second part of the storage period .. suggesting that RBCs are more vulnerable to warming by the end of storage'[11]. Perry et al on the other hand argues that the timeframe for exposure should be decreased, partly due to the fact that there are a vast range of erythrocyte products, in different sizes available, which affects the warming process [12]. Another issue that have been addressed is in what way older blood affect the receiving patient in an transfusion situation and there are signs that at massive transfusions of older blood could in fact constitute a risk factor [4].

1.2   Problem Discussion

However, even though the demands and regulations are quite clear about the ambition and demands on storage and transportation of erythrocytes there are today uncertainties about the actual temperature that affects the blood bags during its shelf life. And even today blood units all over the world are transported to different health care sites without a guaranteed quality control of the required cold-chain. Professionals within the field are operating without full knowledge, sort of in a 'dark-room' [13].

Estimation of temperature deviation in storage and transport is largely based on a 'precautionary principle' due to the fact that studies so far have been difficult to plan which results in the lack of scientific evidence. Probably this leads to the discarding of blood components unnecessarily and the use of blood components which should not be used, due to an insufficient knowledge of the actual state [13].

'We need to distinguish between serious and minor temperature deviations. We need to primarily identify the real situation in our businesses' [13].

With better knowledge about the actual situation that affects the blood bags will the possibilities to develop better processes, minimize risks and optimize the handling of blood bag probably increase.

1.3 Quality of RBC Due to Time and Temperature

The understanding that blood is a sensitive commodity is widely accepted in the field of transfusion. Research as far back as to the fifties address the issue of the aging of blood, how time and temperature affects the blood both in vitro and in vivo and what consequences this bring to the outcome for the patient. And this field of interest seems to be of increased value and interest [4, 9, 14].

Even though there are a vast knowledge about some of the effects, presented below, that time and temperature have on erythrocytes there are today not an overall consensus for how sensitive this makes the blood. There are however an acceptance that blood is a very complex tissue, that will be affected in different ways, and that the final outcome in vivo depends on multiple factors and that extensive research need to be done [4].

1.3.1 Storage Lesions

There is evidence that the erythrocytes will be affected in vitro during storage, i.e. storage lesions. The most influential storage lesions consists of; among others; decreased pH, increase of potassium and lactate, reduction of ATP and 2,3-DPG which leads to an increased rigidity and deformability and eventually haemolysis. The effects storage lesions have in vitro could be divided into; decreased oxygenation capacity, release of damaging components and hindered circulation capacity. There are also evidence that the effects of storage lesions will increase over time and when RBC are stored in too high or too low temperatures [1, 4, 9, 10, 14, 15].

1.3.1.1 Decreased pH

A decreased pH within the RBC will affect cell function partly by the change in conditions of the cell proteins that will be displaced from its optimum in function at pH 7.4. The lower pH of the cell will also consequently increase the affinity of oxygen inside the blood cell which results in a decrease in release of oxygen to the surrounding tissues.

1.3.1.2 Reduced Release of Nitric Oxide, NO by Erythrocytes

In the blood stream Nitric Oxide, NO, released by the erythrocytes affects the local vasodilation of the vessels. With lower oxygen pressure the release of NO rises which in turn leads to increased local vasodilation and also the availability of erythrocytes to pass by and release oxygen. Within the stored RBC detected loss of S-nitrosothiol-haemoglobin (SNO-Hb) after a few days has been shown to diminish the release of NO and also the vasodilative action [1].

1.3.1.3 Decrease of Potassium and Increase of Lactate Within the RBC

Under normal circumstances the level of potassium within the cell is in balance between a passive leakage over the cell membrane and the Sodium-Potassium Pump, (Na+/K+ pump). During storage this pump will become almost inactive under +4 degrees temperature. This leads to a vast outflow of K+ from the cell to the cell medium which could lead to server consequences as heart failure, arrhythmia and paralysis, for the recipient, especially infants and newborns. The inactive pump mechanism also leads to a decrease in the exit transport of lactate from the RBC which in turn lowers the pH [1, 4, 16, 17].

1.3.1.4 Reduction of 2, 3-DPG and ATP

Oxygen binds to hemoglobin and it subsequently creates a change in conformation to the hemoglobin to which it binds in a way that the hemoglobin affinity for extra oxy-

gen increases. 2, 3-Diphosphoglycerate, 2, 3-DPG within the erythrocyte decease the adherence of oxygen to the hemoglobin's of the erythrocyte and consequently the release of oxygen. During storage the levels of 2, 3-DPG, will rapidly decrease, probably due to an active phosphatase. The consequence of low levels of 2, 3-DPG is that the oxygen binds tighter to the hemoglobin. This result in that the transport of oxygen into tissue will be complicated as the release of oxygen from the hemoglobin is getting more difficult [1, 2, 4].

Also the levels of Adenosine triphosphate, ATP, will diminish during storage. The role of ATP are among other as a carrier of energy and facilitates the flexibility of the cell membrane, increases the viability of the cell and possess vasodilating properties [4].

1.3.1.5 Increased Rigidity and Deformability

The decreased flexibility in the membrane leads to an increased rigidity of the erythrocyte. The result hereof will be a notable change of shape which leads to increased deformability and reduced interactions with the endothelial [4]. These morphological changes will be reversed after an early transfusion but will be irreversible at the end of a 42 days storage period [1]. See Figure 1.

Figure 1 The Change of Shape of The Erythrocytes During Storage [2].

1.3.1.6 Haemolysis

Eventually the RBC will hemolyse. This hemolyse is a consequence of an increase of parts of the RBCs that forms clusters and an increase of oxidation of the cell mem-

brane. Due to the hemolysis there will be an increase of free hemoglobin within the erythrocyte package. This free hemoglobin will bind and inactivate NO within the blood bag as well as in the endothelia and increase the vasoconstriction and further decrease the functions of RBC within the bloodstream [1, 4].

1.3.2 Bacterial Growth

The reactions due to transfusion of contaminated RBCs tend to be severe since they usually are concomitant with infused endotoxin, the Gram-negative bacteria's lipo-polysaccharide, which causes the immense release of cytokines. The release of cyto-kines results in major septical reactions as high fever, hypotension and nausea [18].

About one out of 30 000 blood bags are estimated to be contaminated with bacteria and in one out of 500 000 this results in a septical reaction and in one of 10 million this will result in a fatal reaction [18].

The vast majority of bacterial growths are though unlikely to occur below 10 degrees Celsius as they are unable to survive or perish at these temperatures even though some Gram-negative bacteria still could thrive under these conditions.

If the RBCs are stored in a to high temperature, above 10 degrees, there are re-searches that find an increased risk that the bacterial growth will occur [18] but there are also studies that shows that that probability is overrated [19].

1.3.3 Action to Improve the Storage Conditions

The RBC are commonly stored in Europe within an additive solution containing So-dium Chloride, Adenine, Glucose and Mannitol, (SAGM) to counteract the degrad-ing and ageing of the erythrocytes. Each of the ingredients is added for a specific purpose; Sodium Chloride gives isotonicity, Adenine provides ATP, Glucose for the metabolism and Mannitol to halt the hemolysis. [14, 20].

To reduce the probability of bacteria entering the RBCs and to prevent the bacterial growth, routines have been implemented to enhance the disinfection of the donor arm and one have also developed a closed system production process with a sample diversion pouch [19].

1.4 Regulation and Standards

The process of blood components and the following blood transfusion are valued as a transplantation of living organs. The handling of blood bags are therefore strictly regulated by the authorities globally on an international level as well as on a national level. There are therefore similarities but as well differences between the different national legislations. Internationally there are initiatives and organizations as the World Health Organization (WHO) and The International Society of Blood Transfusion (ISBT) and the International Federation of Red Cross and Red Crescent Societies (IFRC) described below, that strives to enhance collaboration and exchange of experiences as well as standardize the process and legislations internationally.

1.4.1 European Union

The co-operation concerning blood transfusion between different member states in Europe was initiated in the 1950s. A steering committee, European Committee on Blood Transfusion (CD-P-TS), within the European Directorate for Quality of Medicines and HealtCare (EDQM) is responsible of steering and coordinating the activities concerning blood transfusion. There are also an expert committee, the Committee on Quality Assurance in Blood Transfusion Services (GTS) [6, 21]. They are guided by the following principles; promotion of voluntary, non-remunerated blood donation, mutual assistance, optimal use of blood and blood products, and protection of the donor and recipient. [6, 21].

The regulation valid to storage, transport and distribution conditions for blood and blood components are specified within the Commissions Directive 2004/33/EG, Annex IV [22].

The steering committee will publish with regularity the 'Guide to the preparation, use and quality assurance of blood components'. This guide considers and takes into account the Councils of Europe's resolutions and recommendations within the field and are to be seen as the generally accepted European standard. All member states should '… take all necessary measures and steps to ensure that the preparation, use and quality control of blood components are carried out in accordance with the guidelines…' [6].

1.4.2 Sweden

On a Swedish national level the blood bank establishment is since 1th of June, 2013, under the governance of the Health and Social Care Inspectorate, IVO. In order to conduct a blood establishment authorization from and an ongoing reporting to the IVO is required. [23].

The legislations valid are 'SOSFS 2009:28, Socialstyrelsens föreskrifter om blodverksamhet' that complements the law (1995:831) on transplantation and the law (2006:496) on security of blood.

These regulations have been interpreted by the Swedish Society for Transfusion Medicine, Svensk Förening för Transfusionsmedicin, to the Swedish Manual for Blood Centers, Handbok för Blodcentraler. This manual are recommended to be used (and are used) by the different Swedish municipalities and blood bank institutions that handles blood components [7].

1.4.3 The International Society of Blood Transfusion (ISBT)

The International Society of Blood Transfusion (ISBT) is an international society with members from over 100 countries that aims to 'Facilitating knowledge about transfusion medicine to serve the interests of donors and patients'. They strive to facilitate international accepted standards for the transfusion medicine industry as well as educational materials and events with a global perspective [24].

ISBT was also the organization that initiated the intercontinental blood labeling system ISBT 128. 'ISBT 128 is the international information standard that defines data structures, barcode placement, product definitions and nomenclature databases for transfusion and transplantation.' [25]. ISBT 128 is thereby the foundation for the labeling of blood bags in Sweden.

1.4.4 The World Health Organization (WHO)

Since 1975 the World Health Organization has been engaged in the process to enhance the safety of blood on a global level. Their Blood Transfusion Safety Programme aims at 'ensure provision of universal access to safe, quality and efficacious blood and blood products for transfusion, their safe and appropriate use, and also ensuring blood donor and patient safety'[26]. They work among others through recommendations, policy advice, technical guidance and also funding support for their member states [26, 27].

1.4.5 International Federation of Red Cross and Red Crescent Societies (IFRC)

IFRC aim is together with the WHO 'to develop a global framework to help achieve 100 per cent voluntary blood donation in every country'[28]. Today this is accomplished in about 50 countries. The IFRC works with the different countries ministries

of health usually with the questions of education and recruitments of residents to voluntary blood donations [28].

1.4.6 Shelf Life

The time period that the blood bags could be stored varies between regions. In the EU and northern America it is defined as the time after which approximately 75% of transfused erythrocytes will survive in the recipient's blood 24 h post transfusion. This time frame is dependent on the additive solution used, in Europe SAGM, and is most often 42 days. This limited time frame though has implications for the blood banks as shortage situations will sometimes occur, in particular at the regions of the major cities, when donors are celebrating holidays away from home. An extended duration due to better storage and new solutions would probably even out these seasonal effects [1, 6, 22].

1.4.6.1 Storage Temperature

Due to legislation as well as praxis has an '30 minutes rule' been established, that limits the time a RBC could be exposed to uncontrolled temperature above 10°C. After his 30 minutes the RBC should not be returned to the blood bank for further distribution. This is set to prevent the RBC from being contaminated with bacterial growth. The background to this rule is the time it takes for the RBC to reaches a 'core temperature' of 10°C, which is determined to affect the rate of bacterial growth as well as the quality of the RBC. This '30 minutes rule' has recently been challenged and proposed to be extended to a '60 minutes rule' with the argument that it was created in the early seventies on whole blood and not on modern containers with additive solutions. More recent research also imply that the RBCs aren't affected negatively with bacterial contamination if exposed to a warmer environment for up to 60 minutes. [10, 18, 29, 30]. There are however others that find the '30 minutes

rule' as to generous as there are a vast range of RBC products, among others smaller blood bags for pediatric use, that will reach a core temperature above the recommended 10 degrees significantly faster than earlier estimated. A suggested solution to the problem is a policy there only RBC products '…that have reached a temperatures of greater than 10°C, using established methods to measure the surface temperature' are deleted [12].

In accordance with this '30 minutes rule' the Swedish Manual for Blood Centers in chapter 6 stipulates that 'Red blood cell units that are normally stored at 2-6°C may be kept until the expiration date if the temperature during 24 hours has exceeded 6°C but not 10°C.' [7].

1.4.7   Transportation of Blood

The 'Commissions Directive 2004/33/EG, Appendix IV' states that 'Transport and distribution of blood and blood components at all stages of the transfusion chain must be under conditions that maintain the integrity of the product' [22].

The Councils 'Guide to the preparation, use and quality assurance of blood components' construes this in its principles chapter 4, paragraph 15. Transportation of blood components that 'It is recommended that some form of temperature indicator be used to monitor the in transit temperature' and that 'Validated transport systems should ensure that at the end of a maximum transit time of 24 hours the temperature should not have exceeded +10°C' [6].

In Sweden the Swedish Manual for Blood Centrals in chapter 6 stipulates that 'Blood units must be transported in such a way that the desired quality is maintained. At transport, the same temperature are required as for stationary storage' [7].

1.5   Wireless Sensor Technology

Back in the nineties when the ISBT 128 standard was introduced it was foreseen that the bar codes should be complemented by digital devices to gather and carry information. Even though the development, adoption and acceptance of the technology not have reached to its potential as soon as estimated, the potentials have not been ignored by the blood banks and transfusion industry [31-36].

The use of wireless technology to the surveillance of the blood bags could provide professionals with an enhanced and easier access to critical medical information. The benefit for the patient as well as the professional should then be a safer, more efficient and qualitative care. Some of the benefits that could be reached are the replacement of manual documentation by electronic documentation as well as automatic identification, tracking and status monitoring of blood products from vein-to-vein in all of the stages in the production chain [31, 32, 36, 37]. Obviously even though the increased effectiveness is appealing when calculating on the return of the investment the overall safety for the patient and the reduced risk for human errors, i.e. mismatch of samples, mismatch at the bedside, could and should be the goal to achieve at for the transfusion organization [31, 38].

With the entrance and acceptance of modern wireless technology, minimal exact thermometers, mobile positioning system and energy efficient microcomputers conditions are set to monitor, gather and distribute information about actual ambient settings. This makes it possible to increase the quality and even the security for the patient [34].

1.6   Wireless Temperature Surveillance

At Karolinska Sjukhuset, Hud-dinge, a systematic monitoring of their internal transports are conducted in
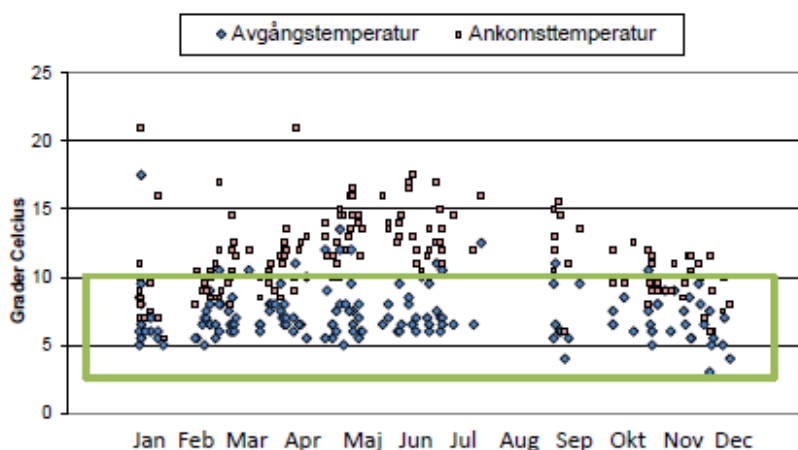
Figure 2 Temperatures at Internal Transports at KS Huddinge, 2012 [1].

line with the Swedish Guidelines and as a part of their process of continuously quality improvement by measuring randomly selected blood transports through out the year. During a year one monitors at an average 150 transports of depot blood in cold environement. During 2012 a discrepancy of the temperatures, between the temperature at the departure and the temperature at the arrival, were identified. The 2012 surveillance showed that only 35% of the shipments were within the applicable quality limit below 10°C. There was also a noteworthy correlation of seasonal effects were the end temperature noticeable increased during the warmer month of May, June and July, see Figure 2 [39].

To falsify the earlier findings a new se-ries of measuments were performed during June 2013.
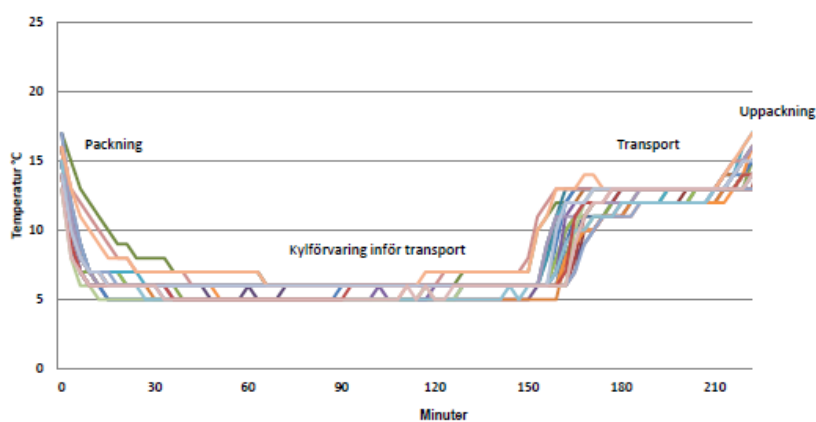
Figure 3 RBC Temperatures at Internal Transports at KS Huddinge, June 2013 [1].

87 RBCs from two

blood centers through the course of three internal transports were monitored. All of these shipments were outside the recommended temperature range of 10°C, see Figure 3 [39].

1.7   Purpose

The purpose of this thesis is to, through a quantitative gatehering of information, explore the actual temperature deviations from standards, during internal storage and internal transports of red blood cell units during its actual shelf life in its real environment.

2 Materials and Methodology

2.1 Literature Study

A literature study was conducted thru the website of University of Gothenburg by PubMed/MEDLINE. The author also used the search engine of Google to complement the information retrieved. The author focused on 'the quality of blood during storage', 'storage lesions and bacterial growth during storage of blood', 'lean production' and 'wireless real time monitoring'.

2.2 Study design

A nonexperimental, described research design were used as the objective of the testest not were to establish a cause-and-effect relation but to record the presence of certain variables[40]. A quantitative approach were used as quality is quantified and where the researcher emphasizes measuring the extent of occasions [41]. The author used the QTA Tracer System® to monitor the environment of bags of erythrocytes during internal transports and internal storages. The data collected were examined with Microsoft Excel to identify the real surrounding temperatures of the blood bags.

2.3 QTA Tracer System®

The system used to gather the information, log the temperature and time of blood bags in this study, was the QTA Tracer System® a sort of Laboratory Inventory Management System (LIMS) developed by the Swedish company Tridentify AB. The system consists of five parts; (Figure 4) the Tracer, the Access
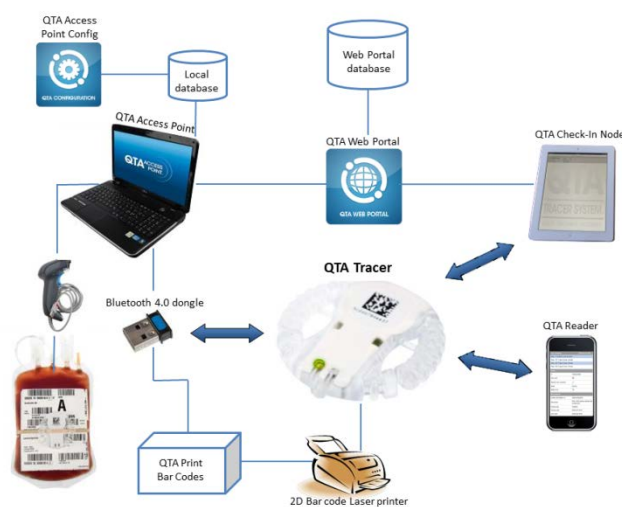
Figure 4. QTA Tracer System® - Overview

Point, the Check-In Node, the Web Portal and the Reader. The system is developed solely to monitor and enhance a good inventory management of blood bags. The system is CE marked in Europe as a Medical Device Class II by the Notified Body of the Technical Research Institute of Sweden, SP. The system is also patented in Europe and the US [42].

2.3.1 The Tracer

The system revolves around the tracer that is mounted on the blood bag and monitors its surface temperature. In its easiest form the user interacts with QTA tracer by turning the tracer their hand and LED's displays if the blood is ok (green light) or not ok (red light).

The tracer is the collector and generator of information, a mobile data logging carrier, the size of Ø55mm x 9 mm (Figure 5). Built on the Texas Instrument, CC2540, a low-power, system-on-chip (SoC) for Bluetooth low energy applications. It consists among others of the Texas Instrument TMP112 digital temperature sensor, the Panasonic battery, the connectBlue OLP425 platform that process the algorithm, the MEMS LIS3DH low-power 3-axis linear accelerometer and two LED-diodes that indicates status of the blood with a red or green light. The tracer measures temperatures in the range of -40 to +60°C. It receive and transfer information wireless with Bluetooth 4.0® to the Access Point,

Figure 5. QTA Tracer Attached to Blood Bag

the Check In Node or the Reader [42]. See also Appendix 1. QTA Tracer Hardware Specifications.

2.3.2 The Access Point

The Access Point is a software installed and running on an ordinary PC that is equipped with a QTA Bluetooth USB dongle and a 2D hand scanner. This is the communication hub with multiple functions. At the Access Point the Tracer will be paired with, 'married to', a specific blood bag. This is also the software were the configuration of time and temperature ranges of the algorithm used to calculate the actual expiration date for the blood bags are specified. This information is then uploaded to the Tracer [42].

After scanning a tracer the access point provides more extensive information from the tracer to analyze it. It facilitates also the information transfer from the tracer to the Web Portal for fully detailed information analyze.

2.3.3 The Web Portal

The Web Portal contains all the information generated from of all the tracers within an organization. The information gathered from the tracers through the access point and the check-in nodes allows the user to sort out tracer specific information on a range of variables as storage and transport location, blood type, status of blood bags, change of status and more [42].

The Web Portal is used to analyze the big data generated within the system. This is either done in the portal or after that the complete temperature vs. time logs for selected blood bags has been exported.

2.3.4 The Check-In Node

The Check-In Node is an app designed to be running on IPads (4th generation or later) or an IPhone 4S (or later) and is dependent on Bluetooth 4.0. It continuously registers tracers that are being moved within a radius of ten meters. The information registered from the tracer, actual blood validity and expiration date, are immediately transferred to the Web Portal over Wi-Fi or over the 3G net together with the GPS location of the Check-In Node [42].

2.3.5 The Reader

The Reader is an application designed for the IPhone 4S (or later) that allows one to scan a blood bag independently of location to extract information on the actual status of a specific blood bag on site. During the work with this thesis the possible information to analyze were current expiration date of the blood bag and the estimated time left when stored in various temperature ranges [42].

2.4   Selection of Respondents and Sites

We introduced QTA Tracer System® to explore the actual temperature variation during storage and deliverance of blood units during its actual shelf life in its real environment. The pilot was implemented at the Transfusion Medicine at Ryhov County Hospital where over 13,000 blood donations are made every year. The Blood Center serves all of the three emergency hospital within the Jönköping's County with a total of about 1 200 patient beds. The establishment is accredited by SWEDAC to ensure its high quality standard of analysis and organization [3, 43].

The fact that the Blood Center at Ryhov County Hospital nurtured an ambition to evaluate and develop its daily routines to ensure a safer production, storage and de-

liverance of RBC to its patients as well as the location and size of the Blood Bank and its yearly production was considered as suitable for this initial study.

2.5 Collecting and Processing of Data with QTA Tracer System®

2.5.1 Manufacturing of Blood Bags at Jönköping Blood Center

At Jönköping blood center the manufacturing process of blood bags consist of the following main processes from donation to transfusion, from vein-to-vein. *Collection*, *Screening*, *Production*, *Storage and Distribution incl. Order Processing*, *Order Allocation and Shipping*, *Transfusion* or *Return Reconciliation*, and *Disposal* (Figure 6).
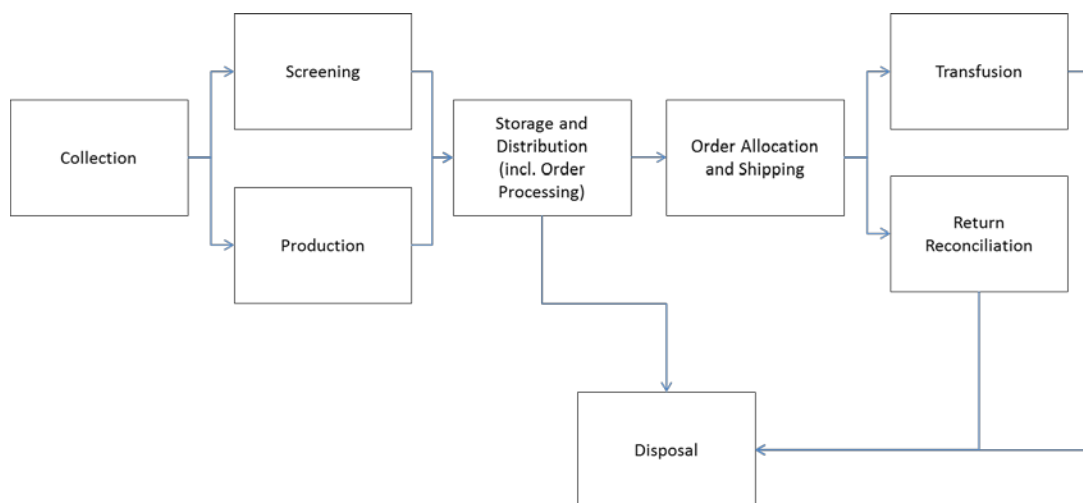
Figure 6. Adapted Top-level Process Flow for Ryhov Blood Center [33].

2.5.1.1 Collection

The County of Jönköping has of today six regular collection sites and one mobile unit. At the collection site the donor will be registered, fill in a digital questionnaire and pass a basic interview covering the donor's health's condition as well as lifestyle and travel activities. If find possible to donate, an amount of about 450 ml blood will

be collected from the donor, this amount is divided into two portions, one blood bag and a tree test tubes for clinical tests. At the donor site the blood will immediately be initially Hb tested and the result will be discussed with the donor. Both the bag and the test tubes will immediately be labeled with bar codes for correct identification in the process. The bags are here marked with the Tap number, Blood Type and Tap date.

When the collection is done outside the County Hospital of Ryhov, both the test tubes and the whole blood bags will be inbound transported to the laboratory and the blood center at the County Hospital.

2.5.1.2 Screening

The test tubes are transported to the laboratory to be tested in accordance with the guidelines. The test consists of the donors Hb and blood type. Also tests for HBsAg, anti-HCV, anti-HIV 1+2 and antibodies to syphilis. The tests tubes are extracted from the closed systems test pouch before the actual tapping is done.

2.5.1.3 Production

The whole blood bag will be processed within the blood center. It will be fractioned thru centrifugation and divided in its portion of red blood cell concentrate, plasma and platelets. Finally here each product will be labeled in accordance with the ISBT 128 bar codes standard and registered in ProSang, the administrative system used. The additional bar codes are; Component code and Expiration date. Together with Tap number, Blood type, and Tap date these make up to the five ISBT 128 bar codes used.

2.5.1.4 Quarantine, Storage and Distribution incl. Order Processing

After processing are the blood bags stored in a therefore designated quarantine re-frigerator to be released after negative test results in the screening process. When re-

leased the blood bag is transferred to one of three storage fridges or transported to the subsidiaries in Värnamo.

When an order is placed, in written, a suitable blood bag is identified due to its typing, and actual date of production or expected date of expiration. The actual blood bag will be matched to the phenotype of the receiver's blood to ensure that no miss match will occur due to difference in ABO type and RH type. One tests for the presence of ABO antigens and ABO antibodies (plasma grouping) as well as RhD antigen and the presence of irregular red cell antibodies.

2.5.1.5 Order Allocation and Shipping

When this matching process is in order the selected blood bag will be complemented with a shipping order. The blood bag is then either placed in the fridge to be picked up later or stored in a cool bag with ice to be transported outside the care of the blood center to the actual ward.

2.5.1.6 Transfusion

At the ward the blood bag are stored in its cool bag or a local fridge. When it is suitable the blood bag will eventually be transfused to the recipient after that the patient ID is matched with the actual blood bag to prevent any bedside miss match. The blood bag will often be heated to some degree before transfusion not to cool down the patient too much.

After the transfusion has been done the empty blood bag will be stored in the local fridge. This is done to ensure that the portion of the blood that are left within the bag should be available to further testing if the patient shows any reaction to the blood given.

2.5.1.7 Return Reconciliation

If the blood bag of some reason not will be transfused it will be returned back to the blood center and handed over from one staff member to one of the designated staff at the center. In this process the one handing over the bag will declare that it has been stored correctly and this will noted in ProSang. In each case but especially if one cannot guarantee that the bag has been treated correctly the bag will be ocular inspected and the surface temperature will be noted. Questionable blood bags will further be controlled due to their level of hemolysis. This control are made by storing the blood bags vertically in the refrigerator, to let the erythrocytes sediment, the color of the over most layer are then compared to a color comparator of Haemonetics® and in critical bags will then be checked through the HemoQue Low. Finally will the doctor in charge authorize a re-storage of the bag or discard it.

2.5.1.8 Disposal

There are primarily three reasons to discard a blood bag. At the blood center it could be outdated due to the fact that it has been positive during the initial screening process, that it has been stored for more than 42 days and that on return at the blood center the surface temperature of the blood bag are shown to be to warm. Finally it could be disposed in the care of the transfusion ward as the patient not has shown any reaction to the blood that he or she has received.

2.5.2   Blood Center Implementation

In discussion with the manager of the blood center we agreed that the scoop of this thesis should focus on two areas of interest; *Internal storage* and *Internal transports* as described above. Finally the storage condition within the different refrigerators at the blood center in Jönköping and also the internal transports of blood bags between the blood center in Jönköping and the subsidiary in Värnamo were selected as test

environments. The trials were conducted thru two independent phases during the period from November 2012 to September 2013.

2.5.2.1 QTA Tracer System® Configuration

During these tests the QTA Tracer System were configured based on the blood centers interpretation of the Swedish Guidelines definition in Chapter 4 and 6. The measuring interval was set to a three minutes pace, which means that every third minute a new record of the actual temperature are logged.

2.5.2.2 Storage Condition

During the test phase in total 80 traces were mounted on to 80 blood bags that were placed in one of four refrigerators (Dometic BR400). These bags were placed, five on each shelf, 20 pieces in each fridge, in total 80 tracers in accordance with the arrangement below. The bags with the tracers were placed on every shelf, marked 1-4 (Figure 7) and one in each corner and one in the middle of each shelf, marked 1-5 (Figure 8).

Figure 7. Shelf Identification
in Refrigerators.
Photo. V.Wadskog

Figure 8. QTA Placement on Shelf.
Photo. V.Wadskog.

2.5.2.3 Internal Transports

At the blood center blood bags were combined with QTA Tracers. This moment were done in the Production process presented above.

In May, August and September 2013 the internal transports of blood bags between the BLC in Jönköping and the subsidiary in Värnamo were monitored. These internal transports are a part of the Quarantine, Storage and Distribution incl. Order Processing. Throughout the year there are 'outbound' transports from the blood center in Jönköping to Värnamo with ordered blood. The blood bags are packed together, in one to two layers, sealed off with air-filled bubble plastic on top and above this ice packs.

The bag is sealed and does not open until it reaches its destination in Värnamo, approximately 75 km and 50 minutes later (Figure 9).

In Värnamo, the blood bags the tracers are checked in thru the 'Check-in Node' and simultaneously placed in the distributed fridge.
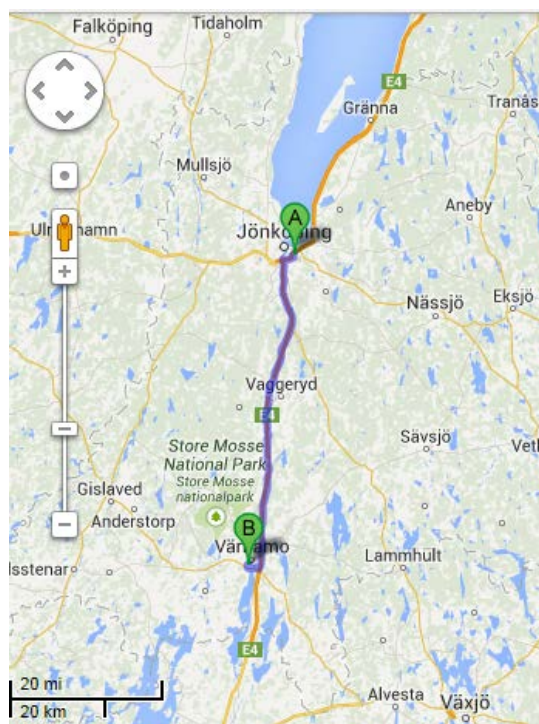
Figure 9. Blood Bag Transportation Route, Jönköping - Värnamo.

2.5.3 Processing of Data

The data collected through the QTA Tracer System® were exported to Microsoft Excel for analysis. One tracer generates one log file that contains the information of

UTC Date Time, Percent Remaining (Life), Temperature. Every third minute a new post is generated.

All the files were examined and the data were sorted on a falling scale of the Temperature. Posts that showed degrees below 2°C or over 10°C were identified and these posts were compared thru time to see if it was deviant from the stipulated standard and expected environment.

2.5.4 Ethics

The scope of this thesis, to gain better information of the actual environmental impact on the blood bag will hopefully result in the development of processes that enables better availability of blood to patient, to gain for the patient.

In accordance with Swedish Law should any research be approved and conducted only if it can be conducted with respect for human dignity and human rights and basic freedoms are heeded [44].

This thesis has been conducted in accordance with the standard operations at the blood center at Ryhov county hospital. The information carried with the QTA Tracer System® involves no information that is traceable to patients in the system. The scarce resource, the blood bags, has not been exposed to extraordinary conditions to gather information.

3 Results

3.1 Empirical Data

3.1.1 Storage Conditions

During the one week period from the 30th of November to the 8th of December 2012 in total 80 (n=80) tracers generated a 306 875 samples. During this week the measured temperatures at 75 positions (n=75), 93.75% were within the specified limit, 2-10°C.

All the specified positions in refrigerator No.1 and No.4 all were within the specified limit.

At nine different occasions the measurements showed a to low temperature under the specified 2°C at five (n=5), 6.25%, of the 80 positions specified.(Figure 10)
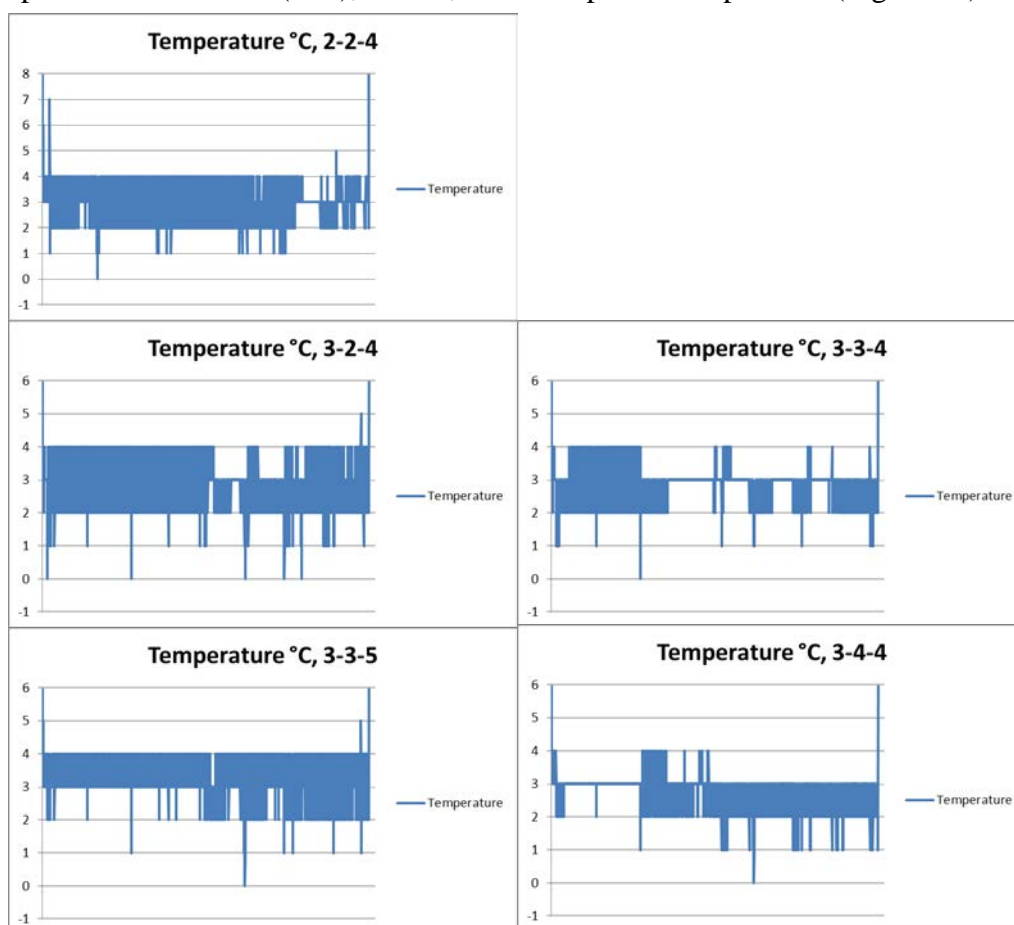

Figure 10. Temperature Deviations of Blood Bags at Storage. On nine different occasions a too low temperature are identified, under the specified 2°C, at five positions.

In fridge No.2, on shelf 2, position 4 (2-2-4) did the temperature at 17 occasions, during 22 intervals, reached below 2°C. As every interval is three minutes, this means that the blood bags at 66 minutes were out of range at this position. At one of these occasions, during one interval, did it reached 0°C, but not below zero.

In fridge No.3, used as quarantine fridge, the temperature reached during 129 intervals below 2°C on four positions, position No.4 on shelf 2, 3 and 4 and also position No.5 on shelf 3. This is equivalent to 387 minutes out of temperature range. Furthermore of these intervals the temperatures reaches 0°C at five different occasions on shelf 2, on position 4. On one of these occasions, also the position No.4 on shelf 3 and 4 reaches 0°C. At no time this is a state for more than two subsequent intervals.

3.1.2 Transport Conditions

The 10th, 14th, 16th and 17th of May and during the period of August to September 2013 were 88 (n=88) blood bags with tracers shipped to Värnamo. At two different shipments did the temperature reached below the lower temperature of 2°C for four, 4,54%, of the marked blood bags.

During the shipment on the 16th of May one blood bag, QTA Tracer No. S00121300556402, reached below 2°C during two hours, between 12:07 and 14:07. From 12:19 to 14:04 the log file shows 0°C.

Again during the shipment on the 27th of August three blood bags reached below 2°C, down to a -1°C.

– Blood bag with tracer No. S00121300975203 was below 2°C between 11:51 and 14:00 during 43 intervals, at 0°C between 11:54 and 13:30 and reached -1°C between 12:03 to 13:33.

– Blood bag with tracer No S00121300976003 was below 2°C between 11:54 to 13:27, 0°C between 11:57 to 12:54 and reached -1°C between 12:03 to 12:21

– Blood bag with tracer No S00121300981403 was below 2°C between 11:53 to 13:38, at 0°C between 11:56 to 13:02 and reached -1°C between 12:02 to 12:26

4 Discussion

4.1 Implications for Clinical Practice

Even though the implications are evident concerning that there are actual deviations from the standards in the physical environments surrounding the blood bags this is a way to small study to draw any general conclusions on any level concerning clinical praxis of the handling process.

Though did the knowledge raised through the evaluations encouraged the blood center on a regional level to change one of their routines, the way the RBCs were packed in cool containers.

- In the cool bags the earlier used air-filled bubble plastic that were used to distant the ice pack from the RBC are now replaced with a sheet of Styrofoam, 3 cm thick.

The increased knowledge of the storage conditions that the positions most exposed to coldness were the innermost ones, above all the position 4, to the left, in the quarantine fridge also led to discussions about the way that RBC were placed in the refrigerators.

- The inner most corner in the fridges will no longer be used to store RBCs. One way to prevent this could be to place plastic baskets in these areas to maintain a proper distant between the RBC and the cool air exhaust.

At all the blood bags that reached below 0°C a control of their level of hemolysis were performed. This control were made by storing the blood bags vertically in the refrigerator, to let the erythrocytes sediment, the color of the over most layer were then compared to a color comparator of Haemonetics®. Only one of the blood bags

reached to level four, and was then tested through the HemoQue Low. All of them had well below the stipulated 0.8% degrees of hemolysis. This fact could raise the question of the 'zero-tolerance' to go below 0°C due to the risk of hemolysis.

4.2   Implications for Future Research

As this is a minor study of the actual environment that the blood bags are exposed to during parts of their shelf life, it would be interesting to further explore this area, with a larger sample group and also on the whole or other parts of the cold-chain as for instance the inbound transports.

In accordance with earlier studies the work with thesis acknowledge the fact that there is a vast range of similar products, with other time and temperature specifications, and the interest to evaluate the actual environment for platelets or whole blood were raised [12].

This thesis focused on some of the internal process at the blood center. Another area of interest that has come to our attention is the actual routines for handling and storage of blood bags in the actual clinical scene, as at the ICU, the surgical department and more.

The apprehension that the RBC sometimes is exposed to high temperature is akonwledged in earlier studies, and there are therefore also a different set of time/temperature range that the RBCs could exposed to. There are in the litteraure also different opinions of the sensitivity of the RBCs to be exposed to to high temperatures [9-11]. With this study we have noticed the fact that the risk for blood bags to be exposed to a too cold environment is not neglectable. The fact that despite this the RBC seems to maintain their quality, at least for a shorter period of time in a zero

degree environment, indicates that this would be of interest for future research to be performed.

During the work with this thesis it has become evident to the author how sensitive the erythrocytes are, how complex the process of producing, storing and distributing blood bags are [1, 4, 7, 9, 10, 14, 15]. It's also the author's opinion that this complex reality has meant that there have been different interpretations of common theoretical standards across both national and international borders because of their experience [5, 7, 8, 22].

An experience made is that this individual degree of interpretation gives certain independence in relation to the Swedish guidelines and maybe even a conscious or unconscious reduced compliance. One reason to this may be that in Sweden, the medical responsible doctor becomes a practical escape route as doctors always can override the theoretical recommendations concerning time and temperature of the blood bags. Another reason may be that the actual temperature/time ratio probably is difficult to accurately estimate. A third reason may be that where you actually do follow-ups, concerning degree of hemolysis, so turns out that rules and recommendations have been set at too high a level of security. One way to enhance the development towards more relevant time/temperature restrictions would probably be to evaluate the affect the time and temperature have on erythrocytes on a larger scale than has been done. The author reason based on this small thesis that this should include warmer as well as colder environment than expected.

One concern of the author was that the experience of using the high level of computer/electronics could have been perceived as complicated for the user or the environment. There were also signs of that in earlier literature concerning introduction of

RFID projects [38]. The author believes, however, that the level of IT maturity in Sweden regarding both mobile phones and computers, and the fact that much has been done in this maturation process the last five years, now made it natural to use this type of technique. One reflection is that almost all literature identified, related to wireless technology, regards RFID and specific readers as the possible solution to the health care organizations even though there now are other standard solutions possible as Bluetooth and handhelds as mobile phones and tablets [31-38].

In preparing this essay the author also identified incidents where individual blood bags were assumed to be correctly stored, but at closer analysis turned out to have been stored for a long time in room temperature. This highlights, the author reasons, the difficulty of actually being able to foresee this process manually since it involves so many people, often under time pressure, that in several stages transfer both blood bags and critical information about the bags. Furthermore, during the course of this work there has been an possible identification of differences between disposals, one within the blood establishment strictly related to the non-achievement of the quality of the blood bags but also one out in operations where loss of blood bags could be due to a general loss due to wrong orders, wrong deliveries or just carelessness.

4.3   Methodological considerations

One aspect of the thesis is that the author did not investigate if there were any specific circumstances that initiated the handling of the refrigerators that caused it to cool down, or if it was just ordinary handling process of the blood bags. If this aspect had been included perhaps some additional insights to the process could have been identified and perhaps also altered to maintain a better storage climate at the quarantine fridge.

Discussion

Earlier studies have focused on the surface- and core temperature of the blood bags and evaluated the quality of the RBC on the behalf of regulations and the 30-minute-rule [10, 12, 29] With this thesis the measurements of the surrounding air temperature ie. suface-temperature are done at a fairly detailed level of three minutes sample rate. This sample rate was chosen together with the blood center at Ryhov as to live up to the standards of monitoring even small deviations from the desired storage temperature. As it turned out with a too cold environment, this narrow tolerance made the tracer sensitive and indicates for 'not valid' at a fairly short period of deviations.

5 Conclusions

The measurements made in this thesis showed that there were actual deviations from the regulated standards in the physical environments surrounding the blood bags, even though the procedures were followed.

To all the blood bags that reached below 0°C a control of their level of hemolysis were performed. The fact that all of them had well below the stipulated 0.8% degrees of hemolysis could raise the question of the 'zero-tolerance' to go below 0°C due to the risk of hemolysis.

The blood center made some minor changes to the procedure of transport packing to reduce the deviations and they also continuously monitor their blood bags to incremental develop their routines.

Populärvetenskaplig sammanfattning

Röda blodkroppar är en viktig del i det moderna sjukvårdssystemet. Cirka 500 000 enheter blod från blodgivare används för framställning av blodkomponenter för blodtransfusion i Sverige varje år. Sverige är idag självförsörjande på blodceller, men tillgången på röda blodceller är knapp.

Hållbarhetstiden för en blodpåse är 42 dagar om den förvaras i en kontrollerad miljö på 2-6°C. Även om krav och regler är tydliga om vad som gäller för lagring och transport av röda blodkroppar finns det idag en osäkerhet kring hur den faktiska temperaturen påverkar blodpåsar under dess livstid. Detta är av stor vikt då det över hela världen transporteras blod mellan olika vårdplatser utan att man idag kan garantera att detta görs i en tillräckligt kyld miljö. Det finns även en begränsad kunskap om hur tid och framför allt temperatur påverkar blodcellerna.

Syftet med uppsatsen var att undersöka den verkliga temperaturvariation för blodpåsar under lagring och transporter under normala förutsättning i en normal miljö. Arbetet visade att det fanns faktiska avvikelser i temperatur för blodpåsarna, vid såväl lagring som transport, även om korrekta förfarandena efterföljdes.

En ovänta upptäckt var att temperaturavvikelserna främst gällde att vissa av blodpåsarna blev för kalla, i vissa fall sjönk temperaturen till under 0°C. Enligt det svenska regelverket så då dessa blodpåsar kasseras.

För alla de blodpåsar som utsattes för temperatur under 0°C genomfördes en kvalitetskontroll för att se hur stor del av de röda blodcellerna som hade förstörts. Dessa påsar uppvisade då med marginal en mindre grad förstörda röda blodceller än det av regelverket godkända 0,8%. Detta faktum påvisar vikten om kunskap om vad som händer med blodet då det idag är "noll-tolerans" för att gå under 0°C eftersom denna

regel annars kan leda till att användbart blod kasseras i onödan. Resultatet medförde också en förändrad transportrutin.

Resultaten påvisar ett behov av bättre kunskap om vilka faktiska temperaturer som blodpåsar utsätts för men också ett stor behov av att förstå vad som händer med blodet vid olika verkliga temperaturer. Med bättre kunskap om verkliga förhållanden kan processer förbättras och utvecklas vilket gör att de donerade blodpåsarna används på bästa sätt. Detta är viktigt ur såväl ekonomiskt som patientsäkerhetsperspektiv.

Testerna genomfördes på blodcentralen vid länssjukhuset Ryhov där QTA Tracer System ® används för att logga verklig tid och temperatur. Tracers fästes på 168 blodpåsar vid produktionstillfället och sedan lagrades dessa i kylskåp och/eller transporteras mellan Jönköping och Värnamo. Loggfilerna analyserades därefter med excel-ark för att identifiera enskilda tracers, blodpåsar, som var utanför tillåtet temperaturområde.

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Appendix 1. QTA Tracer Hardware Specification

The Tracer is based on a sensor module called cB-0950 made by ConnectBlue in Sweden.

The cB-0950 product is a Bluetooth® low energy sensor module. The module is based on the 2.4-GHz Bluetooth® low energy System-on-Chip CC2540 from Texas Instrument (TI) and has an internal antenna. The module is equipped with:

- An temperature sensor (TI TMP112) with max ±0.5°C +0/+65°C, ±1°C -40/+125°C accuracy.
- An accelerometer (ST LIS3DH) which is primary used for detection of module movement but also for wakeup the module by clicking on the module.
- A lithium coin cell BR2330A battery, 3V, 220mAh, Ø23x3mm.
- Battery capacity supervision.
- A red and a green LED.

The module is estimated to have a lifetime of 3 years. The PCB (Printed Circuit Board) size is 22.3x14.8mm and the BR2330A battery is soldered on the side of the PCB. The module has the operating temperature +85/-40 ºC and storage temperature +90/-40ºC but the battery specified up to +125 ºC.

The module is Radio approved for usage in Europe (ETSI), USA (FCC ID: PVH0950) and Canada (IC ID: 5325A-0950) and also Bluetooth Qualified.

Electrical safety

The electronics fulfill:

EMC: EN 301 489-1 V1.8.1 (2008-04), EN 301 489-17 V1.3.2 (2008-04), EN 61000-6-2 (2005)

Health and safety: EN 50371:2002, EN 60950-1:2006 and/or IEC 60950-1:2005 (2nd Edition)

Medical Electric Equipment: IEC 60601-1-2 (2007)