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Implementation of pathogen inactivation by amotosalen plus ultraviolet A illumination for platelets in a national blood service

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Abstract (1) Background: Blood bank stock management of platelet components is especially challenging due to a relatively short shelf live. Pathogen inactivation methods aimed at reducing transfusion of contaminated platelet concentrate (PC) can prolong the shelf life of platelet products. These methods require additional processing that can affect in vitro quality of platelets. In 2012 Intercept pathogen inactivation method by amotosalen plus ultraviolet A illumination was implemented for all platelet production in Iceland. The aim of this work was to investigate the effects on platelet transfusion in Iceland 5 years before and after the implementation; (2) Methods: Data on platelet ordering were extracted from the ProSang blood bank information system. Quality control (QC) data for PC were available from internal QC databases. The number of PC ordered per year, number of PC transfused per patient, PC age (in days) at transfusion, and PC platelet content were compared in two five-year periods, before (2007-2011) and after (2013-2017) implementation of pathogen inactivation (PI) with pathogen inactivation by amotosalen plus ultraviolet A illumination; (3) Results: No significant increase in average overall annual PC transfusions (1819 Pre vs 1890 Pos, p-value > 0,05) or per patient (4,4 PC Pre vs 5.9 Pos, p-value > 0,05) after 5 years of using PI. No significant increase in PC transfusion in all hospital department, excluding Outside hospital department with a significant increase (47,4 Pre vs 117 Pos, p-value < 0,05) after PI implementation. PC available in stock per day increased after PI implementation (16 Pre vs 26 Pos PI, p-value < 0,05) Decrease in number PC delays (6,6 PC per year Pre PI vs 0,2 Pos PI, p-value > 0,05). Rate of outdated PC was not affected (7,12% Pre vs 7,80% Pos PI, p-value > 0,05). A shift was observed in the average age of transfused PC after PI implementation (3.0 days Pre PI vs 4.5 Pos PI, p-value < 0,05); (4) Conclusions: National implementation of pathogen inactivation method for PC production in Iceland did not negatively affect PC transfusion. Implementation had positive effects on PC stock management, with increased availability.

Keywords: platelet concentrates, pathogen inactivation, proteins, cytokines, chemokines, growth factors, platelet storage lesion

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1. Introduction

Donated blood and it´s components are an essential health asset. Overall, there is a high demand for blood products and a small donor pool. As reported by the World Health

Organization (WHO) 118 million blood donations are acquired worldwide. The foremost transfused cluster patients in developed countries is over 60 years old, accounting for up to 75 percent of all transfusions [1]. Blood transfusion in developed countries is mostly for supportive treatment in cardiac surgery, organ transplants, severe trauma, and in therapy for neoplastic diseases of hematopoietic origin the most common indication for platelet transfusion [2–4]. Platelets concentrates (PC) are collected and stored in blood banks to be transfused for actively bleeding patients and as prophylactic for patients with low platelet count. Compared to other blood components stored at subzero or refrigerated temperatures in blood banks, platelets are stored for a relatively short period of 3-5 days at room temperature [5–8].

The restrictions on the shelve life of stored platelets is related to increased risk of bacterial contamination and deterioration of quality during storage referred to as Platelet storage lesion (PSL). Stored at room temperature metabolically active platelets consume nutrients and produce harmful waste products. During storage there is increased production of lactate with elevated levels of pH in the platelet storage media promoting increased platelet activation and general lowering of platelet quality[9–11]. Number of different factors will contribute to the PSL: donor specific, collection, post collection manipulation and the storage conditions [12–17]. In vivo recovery and survival of transfused platelets is correlated with PSL during storage [18,19].

In modern blood banking there has been a inactivation of contaminated blood transfusion due to improvements in aseptic procedures during collection and processing protocols and bacterial screenings. Despite these advances transfusion-transmitted bacterial infections (TTBIs) are still persistent with majority of incidents related to contaminated PC. Septic transfusion reactions (STRs) increase morbidity and have a high mortality rate [20–23]. There is high heterogenicity among studies analyzing the rete of STR making it a challenging task to estimate to true risk of these reactions [23]. Retrospective analysis of PC transfusions implicates that the rate of STRs is likely underestimated [24].

Countries with ageing populations, increased hospitalization and limited donations face an ever more challenging task in meeting harvesting and storage demands [2,25–29]. Ensuring adequate stock and being able to deliver the product fast without delays and limited outdating is challenging especially with this short shelve life of platelets. Modern transfusion medicine demands safe PC products with increased availability.

To address this increase in demand, measures aimed at increasing transfusion safety while prolonging the standard 5-day shelf life of PCs to 7 days have been or are being developed. Several pathogen inactivation (PI) methods using pathogen inactivation (PI) technology are currently available. These utilize ultraviolet (UV) light of different wavelengths with or without photoactive chemicals [30,31]. Amotosalne-UVA (INTERCEPT Blood System, Cerus) represents the most studied and most widely used. Amotosalne-

UVA technology is now in routine use in over 300 blood centers in 40 countries and implemented nationwide in several of them [32–34].

The Reykjavik Blood Bank is a nationwide blood transfusion service in Iceland serving a population of 350.000 inhabitants. Due to Iceland´s unique geographical situation our blood stock management is both a challenge and a matter of public safety. To stabilize the supply of platelet concentrates (PC) and to reduce bacterial contamination risk, pathogen inactivation (PI) of all PC was implemented in 2012. Amotosalne-UVA technology allowed for extension of platelet storage from 5 to 7 days.

The aim of this study is to compare PC transfusion in Iceland in two periods, Pre. (2007-2011) and Pos. (2013-2017) implementation of PI, including number of units transfused per department Pediatric, Emergency, Medicine (Hematology/oncology), Intensive care, Obstetrics, Surgery and outside hospital, age of transfused units and number of units transfused per year and per patient.

2. Results

RESULTS.

PC production and content.

From 2007 to 2017 platelet production in Iceland was on average 2122 PC per year. No significant difference was between the two study periods for overall PC production (2089 Pre vs 2124 Pos, p-value > 0,5 figure 1A). A statistical difference was observed in the BC and apheresis ratios Pre and Pos PR implementation with an increase in apheresis PC´s (58,3 % Pre vs 67,1 % Pos, p-value < 0,05, figure 1B). Apheresis PC contained compatible numbers of platelets per PC product Pre and Post PI implementation (305 x 10^9 platelets. Pre vs 302 x 10^9 platelets. Pos, p-value > 0,05, figure 1C). The BC PC platelet content was significantly lower Pos PI (372 x 10^9 platelets Pre vs 280 x 10^9 platelets Pos, p-value < 0,05, figure 1D)

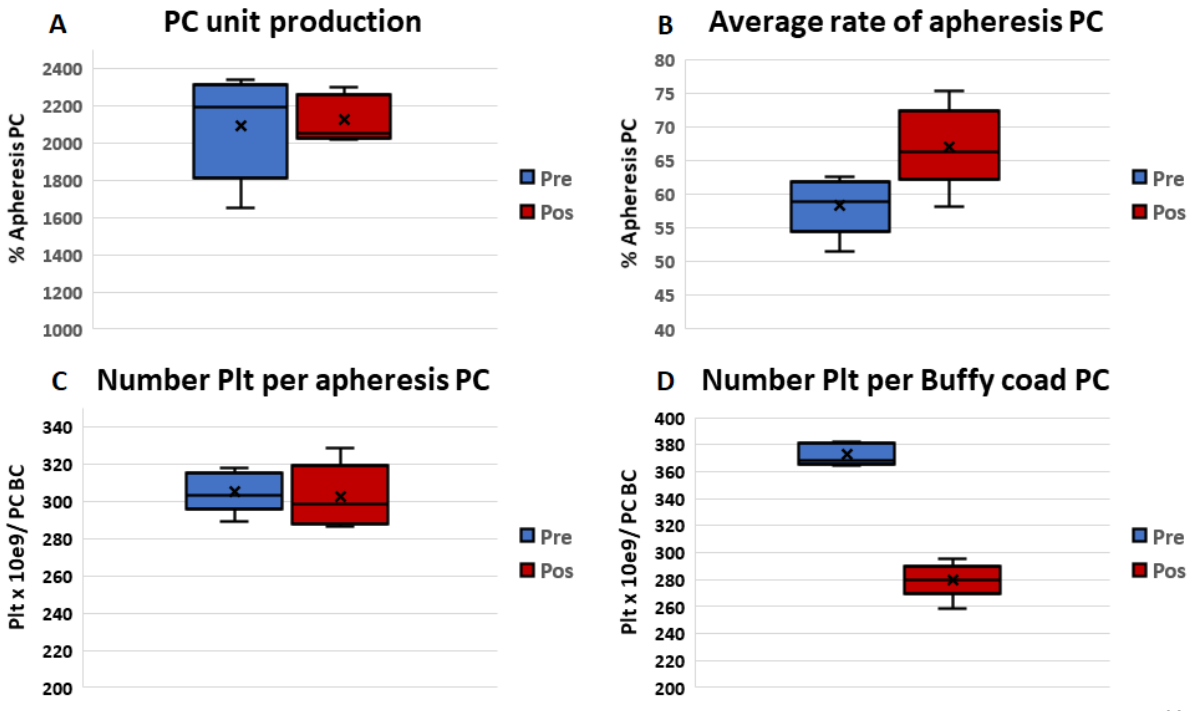

Figure 1. Platelet production Pre PI implemetaion (blue) and post (red). The top and bottom of each box represent the 75th and 25th percentile, respectively, and the central line represents the median. The means are marked with an X, and the outliers with a dot.

PC stock management.

With an increase in the shelve life of the PC product after PI implementation we observed a shift in the age of PC being transfused (3.0 days Pre PI vs 4.5 Pos PI, p-value < 0,05) figure 2. The average number of PC available in stock per day increased after PI implementation (16 Pre vs 26 Pos PI, p-value < 0,05) figure 3 A. Incidents of PC shortage and delayed delivery where more frequent Pre PI (6,6 delayed PC per year Pre PI vs 0,2 Pos PI, p-value > 0,05) figure 3 B. The rate of outdated PC Pre and Pos PI implementation was compatible (7,12% Pre vs 7,80% Pos PI, p-value < 0,05) figure 3 C.

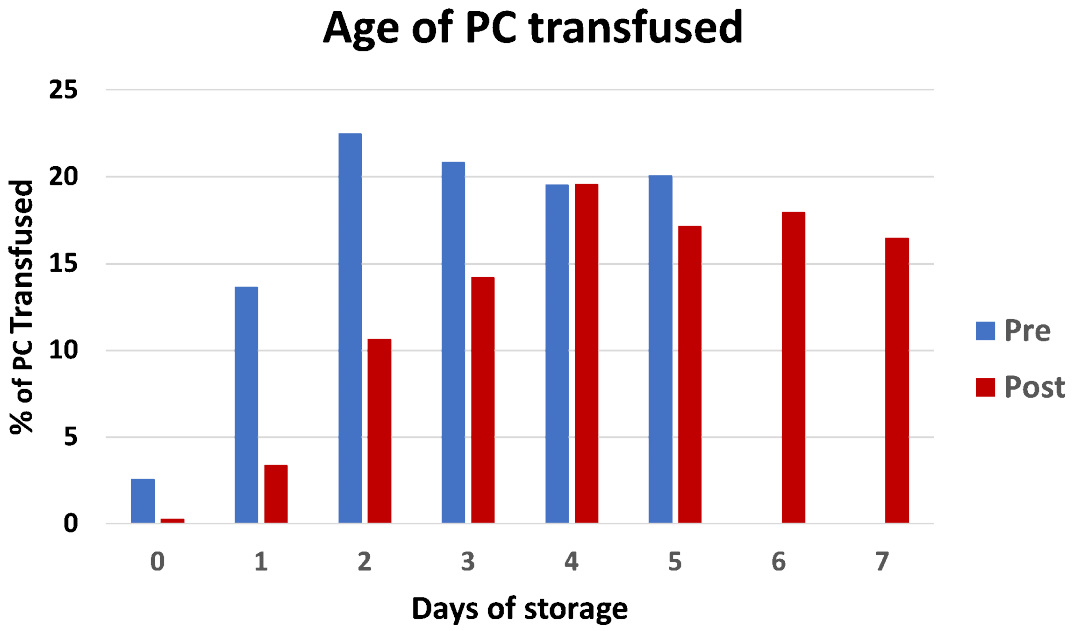

Figure 2. The age in days of PC when transfused. Pre (blue) and Post (red) PI implementation

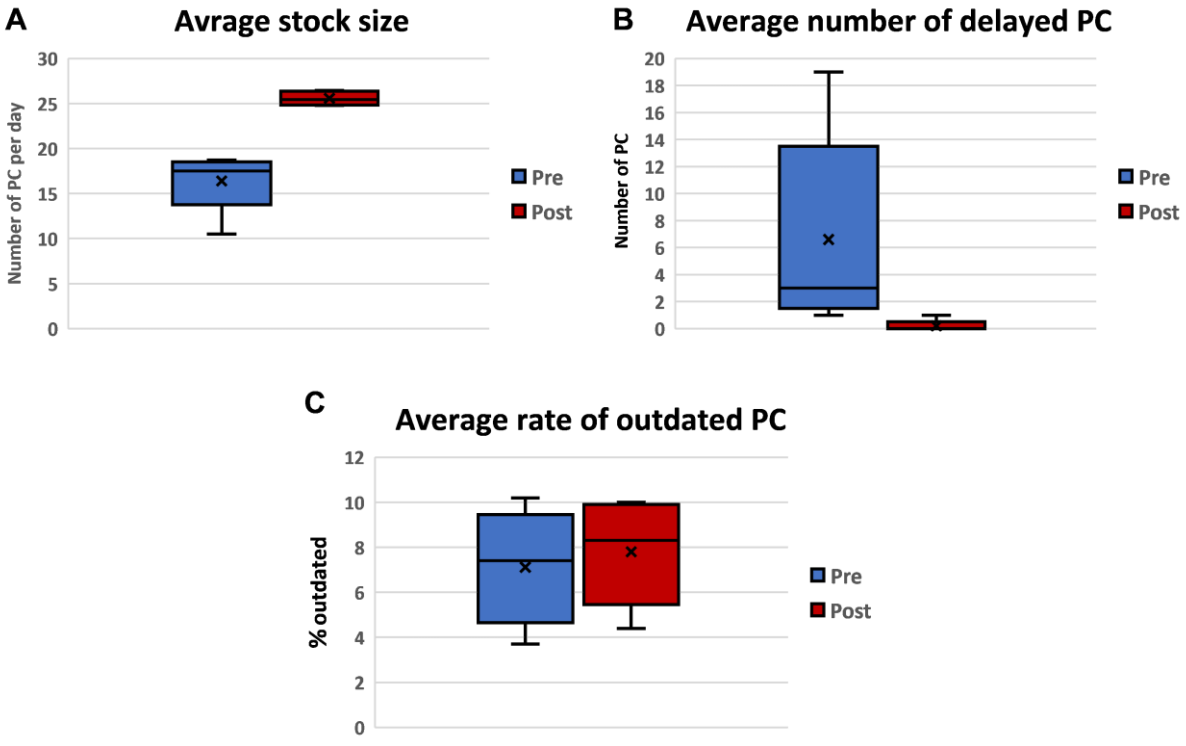

Figure 3. A. Avrage number of PC avilable in stock per day. B. The number of recorded events of dayleayd delevery of PC as a result of PC shortage. C. Rate of outeded PC. Pre (blue) and post (red) implementation. The top and bottom of each box represent the 75th

and 25th percentile, respectively, and the central line represents the median. The means are marked with an X, and the outliers with a dot.

PC transfusion.

There was no significant change in the average number of overall transfused PC (1819 Pre vs 1890 Pos, p-value > 0,05) figure 4 A. Average number of patients receiving PC transfusion (332.8 patients Pre vs 322.6 patients Pos, p-value > 0,05) and number of PC transfused per patient (4,4 PC Pre vs 5.9 Pos, p-value > 0,05) did not change after implementation of PI figure 4. B and C respectively. PC transfusion by location was compatible at all departments except for Outside hospital department with a statistical annual increase (47,4 Pre vs 117 Pos, p-value < 0,05) figure 4. Adverse events recorded related to PC transfusion did not differ pre and pos PI implementation (pre = 3.6 vs pos = 2.6, p-value > 0,05). The rate of PC implicated in adverse events was compatible pre and pos PI implementation (pre = 0,20% vs pos = 0,14%, p-value > 0,05) figure 5.

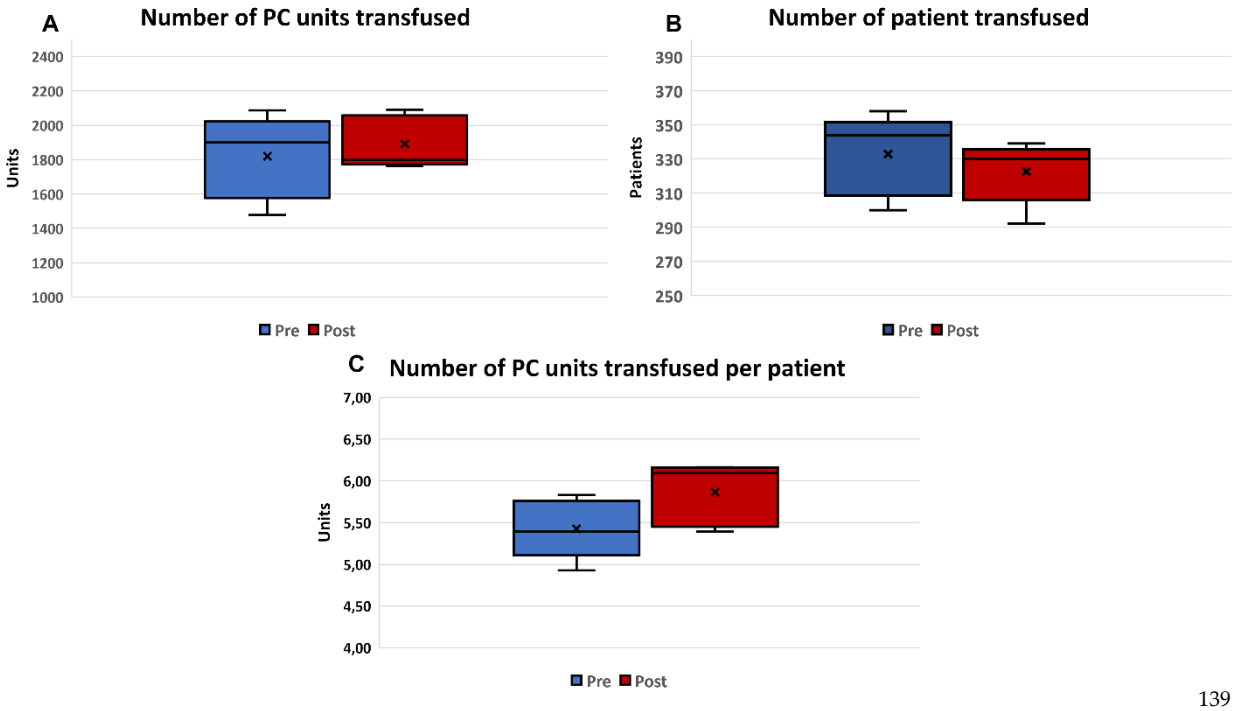

Figure 4. Avrage number of PC transfused. B. The number of patients reciving PC transfusion. C. Rate of outeded PC. Pre (blue) and post (red) implementation. The top and bottom of each box represent the 75th and 25th percentile, respectively, and the central line represents the median. The means are marked with an X, and the outliers with a dot.

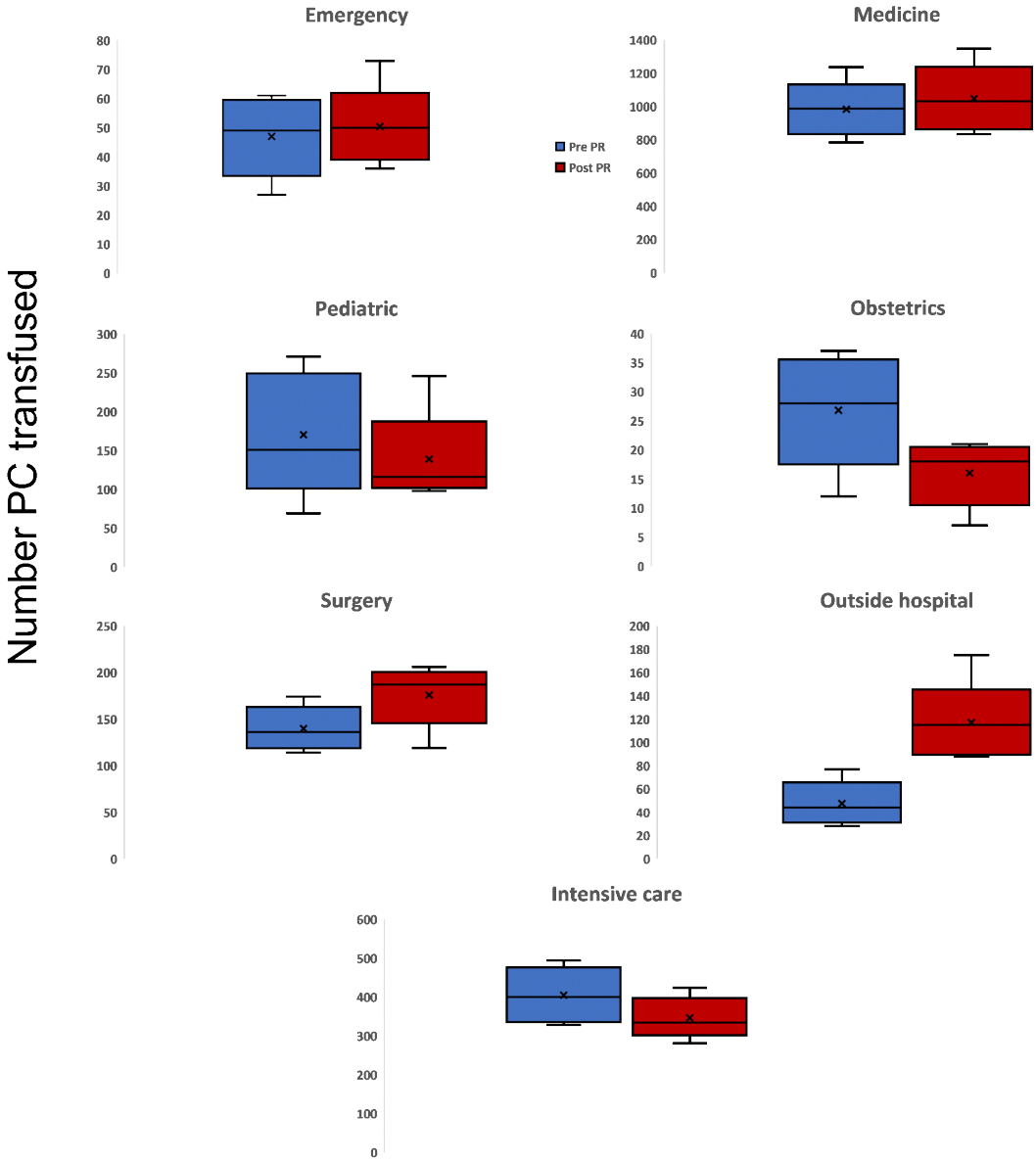

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Figure 5. Number of PC transfusion on avrage anually at slected departments pre and post implemetation 145 146

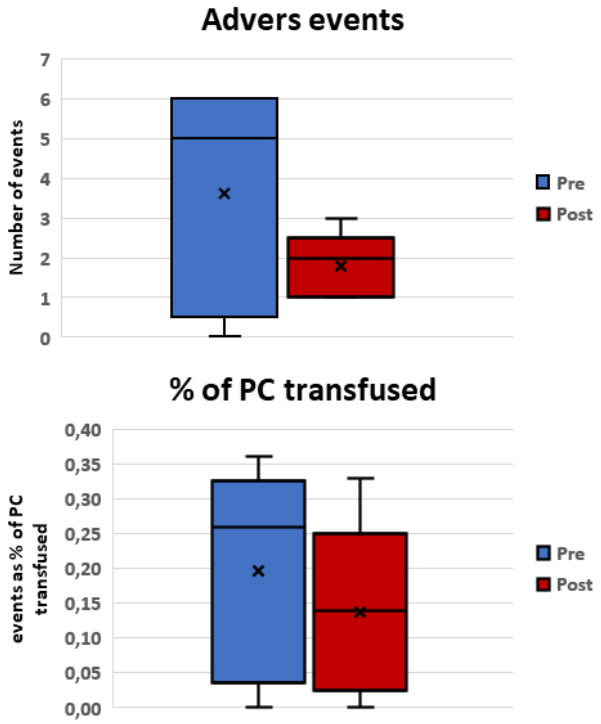

Figure 6. (A) Avrage number of adverse events anually pre and post PI implemetation (B) The avrege portion of all PC anually implacaed in adverse events.

3. Discussion

With the aim of increasing availability and limiting the risk of contaminated PC the Blood Bank of Iceland implemented PI for all PC in 2012. Being the sole provider of PC product in Iceland we sought out to analyze the effect of PI implementation on blood stock management and PC transfusions in a nationwide blood transfusion service. Numerus clinical and retrospective studies on the safety and efficacy of Amotosalne-UVA PI PC have been conducted worldwide with favorable outcome [35–43]. Despite these findings there is still an ongoing debate about the clinical value of implementing amotosalen-UVA pathogen inactivation technology [43,44]. Studies have shown a decreased quality of PI treated platelets at the laboratory level during storage compared to untreated platelets [45–47] Several analyses have been conducted in the past on the effect of PI implementation on platelet utilization with to some extant various results. Infanti et.al conducted a retrospective analysis on platelet utilization at the University hospital in Basil looking at two five-year periods before and after implementation of PI. PI PC had lower (22%) corrected count increments (CCI) than conventional PC. There was a correlation between storage duration and lowering of CCI for both conventional and PI PC. 16.6% of PC transfused after PI implementation were older than 5 days. Despite CCI results there was no change in number of PC per patient or duration of PC support for hematology/oncology and general medical and surgical patients using the majority (92%) of PC after implementation of PI. There was an increase in number of PC per patient and

PC support durations for patients undergoing cardiovascular surgery (CVS) post PI, although a smaller proportion of these patients required RBC transfusion. The opinion of the outers is that this difference does not indicate a lack of efficacy but can be contributed to change in medical practice e.g., viscoelastic hemostatic assays for patient blood management, new emergency protocols and an increasing number of patients on antiplatelet drugs having CVS [48]. Although CCI analysis were not included in our investigation we can speculate there being a lower CCI in the Post PI group as 27% of transfused PC where older than 5 days. CCI analysis alone may not be the best indicator of platelet transfusion efficacy and contribution to patient blood coagulation status. [49]. A systematic review on storage duration up to 7 days of PC transfused for critically ill and hematology patients observed lower CCI for older PC, however there was no effect on the clinical outcome including bleeding, sepsis or mortality [50]. Thromboelastography (TEG) and thromboelastometry (TEM) have gained increased popularity as point of care assays to guide patient blood transfusion management [5152]. Leitner et.al conducted a prospective observational study that showed a significant improvement of TEM parameters after transfusion of pathogen reduced PC in patients receiving hematopoietic stem cell transplants. This post transfusion improvement for the TEM assay did not mandatory correlate with CCI or 1-hour post transfusion increase [53]. In relation to lower CCI of PI PC concerns of inferiority especially in massive transfusion setting have been raised [54]. Nussbaumer et.al analyzed retrospectively the effect of PI implementation on mortality/morbidity and blood component use for massively transfused patients showing no adverse effects of PI implementation. Garban et.al conducted 3 arm analysis comparing conventional PC suspended in PAS or Plasma and PI PC suspended in PAS. There were significantly more transfusion of lower dose PI PC and patients in that arm where more likely to receive a second PC transfusion less than 2 days after the first transfusion compared to the other 2 study arms. There was no statistical difference in the total number of PC transfused per patient. PI treatment of platelets suspended in PAS had no effect on bleeding events. PI PC in PAS where inferior to PC in plasma in relation to (WHO) grade 2 bleeding but not grade 3 or 4. RBC transfusion where compatible in all 3 study arms[42]. Shorter transfusion intervals have been reported in other clinical trials including the SPRINT and euroSPRITE trials conducted to gain approval in the USA and EU [363555]. Even with a potential increase of low-risk bleeding events and shorter transfusion intervals without the increase of PC per patients, these drawbacks must be weighed against the gain of drastically lowering the risk septic transfusion reaction due to transfusion of contaminated PC. Over 875.000 PI PC units have been transfused in France ,Belgium and Switzerland with 0 reports TTBI or fatality's compared to 78 TTBI and 16 fatality's linked to the transfusion of conventional PC [5657]. In our analysis there were 0 reports on TTBI pre or post PI implementation. The fact that there were 0 reported TTBI pre PI in our setting is likely because of overall small number of transfusion and lack of reporting. Reports on other AE where compatible pre and post PI. The most notable difference relating to our experience was the reduction in PC shortage due to larger stock and increased availability made possible by 7-day storage post PI. As a result, there was a shift in the average age of

transfused PC´s from 2.0 day old Pre PI to 4.16 day old Pre PI. Pre PI 83% of transfused PC were stored for 3 days or less this number dropped to 38% after PI implementation. After PI implementation 44% of the transfused PC hand been stored for 5 days or more. With a prolonged PC shelve life a decrease in number of outdated units is expected. In our setting a prolonged shelve life made it possible to increase our PC stock without more outdating. Being the only blood bank located in Iceland PC availability is a matter of public safety.

The two time periods compared were similar in number of patients and PC produced. There was a significantly higher proportion of apheresis PC post PI implementation. In 2014 our facility moved from mixed single and double dose apheresis collections to 100% double dose apheresis collections. A decision to increase single donor apheresis collections in our PC production was made to have more stability on our PC stock. The decrease in platelet content per PC unit after PI implementation relates to changes in processing protocol moving from semi-automatic processing using 5 BC per PC to manual processing with 4 BC per PC. A lower average platelet content did not translate into more PC transfusions post PI implementation. In both study periods the average platelet content per PC unit was well over the $200x10^9$ per unit recommended by the The European Directorate for the Quality of Medicines & HealthCare (EDQM 2020) standard [58]. In our transfusion by location analysis, an increase in transfusions for outside hospital was observed. We categorized outside hospitals as smaller healthcare facilities placed outside the capital Reykjavik and not a part of our national hospital Landspitali University hospital the Blood bank of Iceland main customer. These facilities are especially depended on governmental funding and healthcare policy. Surgery and Obstetrics units can be closed and reopened at any given time at these facilities depending on funding. In fact, this increase in PC transfusions is mainly due to increased activity at two outside hospitals located at Selfoss and Keflavik that had 10 PC transfusion pre PI compared to 263 PC transfusions post PI.

Our experience of PI technology is safe PC product with increased availability, without an increase in number of PC transfusions.

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4. Materials and Methods

Platelet concentration production

Platelet concentrates where collected using Amicus Crescendo (Fresenus Kabi, Lake Zurich, IL, USA) apheresis machine from 2007 until late 2017 when their use was discontinued due to implementations of Trima Accel for platelet apheresis (Terumo BCT, Lakewood, CO, USA). Platelet concentrates were processed from 5 whole blood donation with an automated blood processing system Orbisac (Terumo BCT, Lakewood, CO, USA) from 2007 until implementation of manual Intercept processing in 2012 using 4 whole blood donation per PC unit. Post PI 2007 to 2012 the rate of irradiated PC was on

average 80%. Platelet additive solutions (PAS) used for PC storage was T-Sol (Baxter, Deerfield, IL, USA) pre-PI and SSP+ (Macopharma, Tourcoing, France) post-PI.

Data collection and design

Platelet ordering and outdating data was extracted from electric recording system Prosang version 7.0 (CSAM, Oslo, Norway). Delays in delivery and incidents of low stock where available as deviation recordings in a Lotus notes data base (IBM, Armonk, NY, USA). PC platelet count data was available from in house Excel database. The number of PC transfused per year, Patient population, number of PC transfused per patient and by, PC age (in days) at transfusion, and PC platelet content were compared in two five-year periods, before (2007-2011) and after (2013-2017) implementation of PI. PC transfusion by different location (Emergency, Intensive care, Medicine, Pediatric, Surgery, Outside hospital) was compared between the two time periods.

Statistical analysis.

Data analysis where preformed on Excel 365 (Microsoft, Redmond, WA, USA) Distribution of data using box and whiskers charts. The top and bottom of each box represent the 75th and 25th percentile respectively, and the central line represents the median. The means are marked with an X, and the outliers with a dot. Differences between the two treatment periods were assessed by two-sided t test (with unequal variances) for continuous variables.

Author Contributions: Niels Arni Arnason: data curation, writing—original draft preparation, investigation, conceptualization, and methodology; Ragna Landrö: conceptualization and methodology; Björn Hardarsson: conceptualization and methodology; Sveinn Gudmundsson: conceptualization; Olafur E. Sigurjonsson: supervision, writing, reviewing and editing, conceptualization, and methodology

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Institutional Review Board Statement: The study was approved by the National bioethics committee: VSNb2019100020/03.01

Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflict of interest

References

1. Blood safety and availability. https://www.who.int/news-room/fact-sheets/detail/blood-safety-and-availability.
2. Estcourt, L. J. Why has demand for platelet components increased? A review. *Transfusion Medicine* vol. 24 (2014).
3. Auvinen, M. K. *et al.* Patterns of blood use in Sweden from 2008 to 2017: A nationwide cohort study. *Transfusion* **60**, (2020).
4. Gottschall, J. *et al.* The epidemiology of platelet transfusions: an analysis of platelet use at 12 US hospitals. *Transfusion* **60**, (2020).
5. Schubert, P. & Devine, D. V. Towards targeting platelet storage lesion-related signaling pathways. *Blood Transfusion* vol. 8 (2010).
6. Högman, C. F. Storage of blood components. *Curr. Opin. Hematol.* **6**, (1999).
7. Vollmer, T., Hinse, D., Diekmann, J., Knabbe, C. & Dreier, J. Extension of the Storage Period of Platelet Concentrates in Germany to 5 Days by Bacterial Testing: Is it Worth the Effort? *Transfus. Med. Hemotherapy* **46**, (2019).
8. Satake, M. *et al.* Platelet safety strategies in Japan: impact of short shelf life on the incidence of septic reactions. *Transfusion* **60**, (2020).
9. Kocazeybek, B., Arabaci, Ü., Akdur, H., Sezgiç, M. & Erentürk, S. Prospective evaluation of platelets prepared by single and random methods during 5 days of storage: Aspects related to quality and quantity. *Transfus. Apher. Sci.* **26**, (2002).
10. Akay, O. M., Gündüz, E., Başyiğit, H. & Gulbas, Z. Platelet function testing during 5-day storage of single and random donor plateletpheresis. *Transfus. Apher. Sci.* **36**, (2007).
11. Gulliksson, H. Defining the optimal storage conditions for the long-term storage of platelets. *Transfus. Med. Rev.* **17**, (2003).
12. Devine, D. V. & Serrano, K. The Platelet Storage Lesion. *Clinics in Laboratory Medicine* vol. 30 (2010).
13. Shrivastava, M. The platelet storage lesion. *Transfus. Apher. Sci.* **41**, (2009).
14. Singh, S., Shams Hakimi, C., Jeppsson, A. & Hesse, C. Platelet storage lesion in interim platelet unit concentrates: A comparison with buffy-coat and apheresis concentrates. *Transfus. Apher. Sci.* **56**, (2017).
15. Shams Hakimi, C. *et al.* In vitro assessment of platelet concentrates with multiple electrode aggregometry. *Platelets* **26**, (2015).
16. Waters, L., Cameron, M., Padula, M. P., Marks, D. C. & Johnson, L. Refrigeration, cryopreservation and pathogen inactivation: an updated perspective on platelet storage conditions. *Vox Sanguinis* vol. 113 (2018).
17. Rijkers, M. *et al.* Evaluation of the role of the GPIb-IX-V receptor complex in development of the platelet storage lesion. *Vox Sang.* **111**, (2016).
18. Murphy, S., Sayar, S. N. & Gardner, F. H. Storage of platelet concentrates at 22 degrees C. *Blood* **35**, (1970).
19. SNYDER, E. L. The cellular and molecular basis of the platelet storage lesion: a symposium summary. in *Transfusion* vol. 32 (1992).

20. Pietersz, R. N. I. *et al.* Bacterial contamination in platelet concentrates. *Vox Sanguinis* vol. 106 (2014).
21. Kleinman, S., Reed, W. & Stassinopoulos, A. A patient-oriented risk-benefit analysis of pathogen-inactivated blood components: Application to apheresis platelets in the United States. *Transfusion* **53**, (2013).
22. Spindler-Raffel, E. *et al.* Enlargement of the WHO international repository for platelet transfusion-relevant bacteria reference strains. *Vox Sang.* **112**, (2017).
23. White, S. K., Schmidt, R. L., Walker, B. S. & Metcalf, R. A. Bacterial contamination rate of platelet components by primary culture: a systematic review and meta-analysis. *Transfusion* **60**, (2020).
24. Hong, H. *et al.* Detection of septic transfusion reactions to platelet transfusions by active and passive surveillance. *Blood* **127**, (2016).
25. Newland, A. *et al.* A systematic literature review on the use of platelet transfusions in patients with thrombocytopenia. *Hematol. (United Kingdom)* **24**, (2019).
26. Roh, J., Choi, S. J., Kim, S., Min, H. & Kim, H. O. Blood supply and demand in Korea: What is in store for the future? *Yonsei Med. J.* **61**, (2020).
27. Charlton, A. *et al.* Where did platelets go in 2012? A survey of platelet transfusion practice in the North of England. *Transfus. Med.* **24**, (2014).
28. Shah, A., Stanworth, S. J. & McKechnie, S. Evidence and triggers for the transfusion of blood and blood products. *Anaesthesia* vol. 70 (2015).
29. Mookerjee, S., Foster, H. R., Waller, A. K. & Ghevaert, C. J. In vitro-derived platelets: the challenges we will have to face to assess quality and safety. *Platelets* **31**, (2020).
30. Mohr, H. *et al.* A novel approach to pathogen reduction in platelet concentrates using short-wave ultraviolet light. *Transfusion* **49**, (2009).
31. Pelletier, J. P. R., Transue, S. & Snyder, E. L. Pathogen inactivation techniques. *Best Practice and Research: Clinical Haematology* vol. 19 (2006).
32. Hechler, B. *et al.* Preserved functional and biochemical characteristics of platelet components prepared with amotosalen and ultraviolet A for pathogen inactivation. *Transfusion* **53**, (2013).
33. Jansen, G. A. J. *et al.* Functional characteristics of photochemically treated platelets. *Transfusion* **44**, (2004).
34. Knutson, F. *et al.* A prospective, active haemovigilance study with combined cohort analysis of 19 175 transfusions of platelet components prepared with amotosalen-UVA photochemical treatment. *Vox Sang.* **109**, (2015).
35. Van Rhenen, D. *et al.* Transfusion of pooled buffy coat platelet components prepared with photochemical pathogen inactivation treatment: The euroSPRITE trial. *Blood* **101**, (2003).
36. McCullough, J. *et al.* Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: The SPRINT trial. *Blood* **104**, (2004).
37. Nussbaumer, W. *et al.* Patient outcomes and amotosalen/UVA-treated platelet utilization in massively transfused patients. *Vox Sang.* **112**, (2017).
38. Estcourt, L. J. *et al.* Pathogen-reduced platelets for the prevention of bleeding. *Cochrane Database of Systematic Reviews* vol. 2017 (2017).
39. Cid, J., Escolar, G. & Lozano, M. Therapeutic efficacy of platelet components treated with amotosalen and ultraviolet A pathogen inactivation method: Results of a meta-analysis of randomized controlled trials. *Vox Sang.* **103**, (2012).
40. Slichter, S. J. *et al.* Platelets photochemically treated with amotosalen HCl and ultraviolet A light correct prolonged bleeding times in patients with thrombocytopenia. *Transfusion* **46**, (2006).
41. Lozano, M. *et al.* A multi-centre study of therapeutic efficacy and safety of platelet components treated with amotosalen and ultraviolet A pathogen inactivation stored for 6 or 7d prior to transfusion. *Br. J. Haematol.* **153**, (2011).

42. Garban, F. *et al.* Comparison of the hemostatic efficacy of pathogen-reduced platelets vs Untreated platelets in patients with thrombocytopenia and malignant hematologic diseases: A randomized clinical trial. *JAMA Oncol.* **4**, (2018).
43. Garraud, O. & Lozano, M. Pathogen inactivation/reduction technologies for platelet transfusion: Where do we stand? *Transfusion Clinique et Biologique* vol. 25 (2018).
44. Garraud, O. Pathogen reduction or inactivation technologies for platelet components: Does decision making have to await further clinical trials? *Transfusion and Apheresis Science* vol. 57 (2018).
45. Johnson, L., Loh, Y. S., Kwok, M. & Marks, D. C. In vitro assessment of buffy-coat derived platelet components suspended in SSP+ treated with the INTERCEPT Blood system. *Transfus. Med.* **23**, (2013).
46. Apelseth, T. O. *et al.* In vitro evaluation of metabolic changes and residual platelet responsiveness in photochemical treated and gamma-irradiated single-donor platelet concentrates during long-term storage. *Transfusion* **47**, (2007).
47. Kaiser-Guignard, J. *et al.* The clinical and biological impact of new pathogen inactivation technologies on platelet concentrates. *Blood Rev.* **28**, (2014).
48. Infanti, L. *et al.* Clinical impact of amotosalen-ultraviolet A pathogen-inactivated platelets stored for up to 7 days. *Transfusion* **59**, (2019).
49. Nussbaumer, W. *et al.* Patient outcomes and amotosalen/UVA-treated platelet utilization in massively transfused patients. *Vox Sang.* **112**, 249–256 (2017).
50. Aubron, C., Flint, A. W. J., Ozier, Y. & McQuilten, Z. Platelet storage duration and its clinical and transfusion outcomes: A systematic review. *Critical Care* vol. 22 (2018).
51. Liew-Spilger, A. E. *et al.* Clinical Medicine Viscoelastic Hemostatic Assays for Postpartum Hemorrhage. *J. Clin. Med* 10 (2021) doi:10.3390/jcm10173946.
52. Peng, H. T., Nascimento, B. & Beckett, A. Thromboelastography and Thromboelastometry in Assessment of Fibrinogen Deficiency and Prediction for Transfusion Requirement: A Descriptive Review. (2018) doi:10.1155/2018/7020539.
53. Leitner, G. C. *et al.* The assessment of platelet function by thromboelastometry as a point-of-care test to guide Intercept-treated platelet support in hemato-oncological patients and hematopoietic stem cell transplantation recipients. *Transfusion* **60**, (2020).
54. Hess, J. R., Pagano, M. B., Barbeau, J. D. & Johannson, I. Will pathogen reduction of blood components harm more people than it helps in developed countries? BACKGROUND: Blood-borne infectious diseases are a. doi:10.1111/trf.13512.
55. JL, K. *et al.* Clinical effectiveness of leucoreduced, pooled donor platelet concentrates, stored in plasma or additive solution with and without pathogen reduction. *Br. J. Haematol.* **150**, 209–217 (2010).
56. Safety, Efficacy, and Hemovigilance - HCP Intercept USA. https://hcp.intercept-usa.com/what-is-pathogen-reduction/safety-efficacy-and-hemovigilance/.
57. Levy, J. H., Neal, M. D. & Herman, J. H. Bacterial contamination of platelets for transfusion: strategies for prevention. *Critical Care* vol. 22 (2018).
58. Council of Europe. *Guide to the Preparation, Use and Quality Assurance*. (2020).