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Recent Advances in Platelet Transfusions

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Blood transfusion services have particularly witnessed increasing demands on platelet transfusions in the past two decades. Requests for platelet concentrates (PC) escalated about 191% in the period of 1980 to 1986. This is in comparison with 15% increase in RBC transfusions during the same period. This significant increase in platelet transfusions could be attributed to the overall improvement in health care services, the increased use of intensive chemotherapy for cancer patients and wider performance of sophisticated surgeries like open heart surgery.

In face of this increasing demand on a costly product, it is essential to draw clear guidelines and criteria for the indications of platelet transfusions and to reconsider platelet collection techniques with the goal of optimizing platelet yield.

The cut off point at which platelet transfusions are indicated prophylactically has been debatable. Earlier works[2] suggested a level of $<20 \times 10^9/1$. More recent studies suggested $<5 \times 10^9/1$[3] and $<10 \times 10^9/1$[4]. There is a consensus that prophylactic PC transfusions are indicated for platelet counts $<5 \times 10^9/1$. Counts between $5\text{-}10 \times 10^9/1$ may be considered for prophylactic transfusion according to the clinical judgement. The threshold could be elevated in the presence of platelet dysfunction or severe bleeding. But it is generally agreed that in their absence no prophylactic transfusion is indicated for platelet counts above $10 \times 10^9/1$.

Understanding the kinetics of platelet survival could permit the development of better regimens for platelet transfusions which are more cost-effective. Platelets are known to disappear from the circulation by two different mechanisms; senescence and hemostatic support[5]. Two recent studies have tried to analyze platelet kinetics but came with conflicting conclusions and recommendations. In a recent study by Hersh in 1998, he recommended the use of more frequent smaller dose (3 random donor platelets (RDP) or 1/2 single donor apheresis (SDA)) platelet transfusions with the aim of controlling hemostasis yet reducing the total number of units transfused and the overall cost (4000 $ saving per patient per 100 days)[6]. Different recommendations were reported by Harker[7] who thought that less frequent platelet transfusions of large doses (once every 4-5 days) produce more effective hemostatic control. These recommendations are more convenient to the recipient and the doctor. To improve platelet yield from whole blood, Kelly suggested few simple efficient technical points which will reduce the overall cost of platelet transfusions[8]. Paying attention to technical details of platelet collection like messaging whole blood unit before centrifugation, using liner cups during centrifugation, minimizing time between centrifugation and platelet rich plasma (PRP) or platelet poor plasma (PPP) expression and finally placement of PPP collection satellite bag on a higher level during expression, were found to significantly improve platelet yield. The mean platelet count of these high yield PC was $9.69 \times 10^{10}/1$ compared with average $5.5 \times 10^{10}/1$ for conventional PC. This means that the usual transfusion dose of 6 RDP can be replaced by 4 high yield RDP with resulting reduction in overall cost.

Advances in molecular biology contributed to the recent availability of recombinant growth factors. Of these GM-CSF and the interleukins 1,3,6 and 11 are probably the most relevant in megakaryocytopoeisis. Recent discovery, isolation and cloning of the megakaryocyte specific growth factor, thrombopoeitin (TPO)[9,10], in addition to the above mentioned growth factors may contribute to the overall reduction of platelet transfusions by rapid reconstitution of marrow elements and correction of post-chemotherapy cytopenias.

Similarly, advances in bone marrow transplantation and wider application of cord blood stem cell transplantation may shorten the duration of therapeutically induced cytopenias and thus reduce the overall demand of platelet transfusions.

Despite the above mentioned measures, there is still difficulty in providing large numbers of PC as in military casualties. The short shelf life of PC poses difficulties. There is a need for frozen platelet products and platelet substitutes. This subject is under current research in Bethesda since 1996 being sponsored by the Combact Casualty Care programs and Material command of the USA Army[11]. The menu currently under investigation includes: frozen platelets, freeze dried platelets, thrombospheres, thromboerythrocytes and infusible platelet membranes (IPM). The latter provided encouraging results in phase 1 studies on healthy donors by shortening bleeding time. Phase 2 studies in patients also

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showed favourable results and transient suppression of refractoriness to platelet transfusions. IPM was associated with no serious adverse effects[11]. Despite these early encouraging results, more clinical trials are needed to evaluate the clinical efficacy of these products.

The practice of platelet collection by plateletpheresis has increased in recent years. The relative proportion of SDA has increased in USA from 11% in 1980 to 23% in 1986[11]. In a report from Riyadh[12], the number of SDA increased from 1000/year in 1988 to 2300/year in 1997. Yet in other hospitals in the Gulf region, it is still an infrequently performed procedure.

There is a consensus agreement that SDA are preferable to RDP because they reduce exposure to donors and therefore, recipient alloimmunization and refractoriness to platelet transfusions. On top of that, SDA also permits matching between donor and recipient antigens, and it therefore allows management of refractory cases.

The production of more efficient continuous flow apheresis machines have contributed to development of apheresis. New machines require less anticoagulant, thus produce less side effects[12b]. They also allow faster donation and are therefore more convenient to the donor and the transfusion personnel. In a recent study by Mcleod[13], 17,584 SDA procedures in 17 different centers were reviewed. Donor reactions were infrequent (1.05%) compared with the 9-16% donor reaction rate in whole blood donations[14]. This is partly attributable to less hypovolemia induced by plateletpheresis compared with whole blood donations. Apart from manageable mild tingling sensation and light headedness, the complications most commonly encountered were veinpuncture associated[13].

Quality assessment of platelet transfusion relied heavily in the past on in-vivo evaluation of post-transfusion platelet increments in volunteers and control of bleeding in thrombocytopenic patients. Other means of in-vitro evaluation include the phenomena of swirling[15], platelet morphology, platelet response to hypotonic solution, platelet aggregometry, flowcytometry for platelet surface glycoproteins, and evaluation of platelet adhesion and contractility[10,16,17]. Development of these measures are highly needed as quality tools to optimize platelet collection and storage conditions.

Refractoriness to platelet transfusions is a common complication in patients receiving repeated platelet transfusions like cancer patients on chemotherapy. This problem is probably the most difficult to deal with as far as platelet transfusions are concerned. Patients initially responding adequately to platelet transfusions ultimately fail to show the expected post-transfusion increments in platelet counts. Recipient alloimmunization to donor's HLA class I or platelet alloantigens are important causes of refractoriness. Clinical factors eg. fever, hypertension, DIC and bleeding may also contribute. One of the commonly used criteria to define refractioness is calculation of corrected count increment (CCI)* at one hour. CCI value of less than 10,000 µl indicates refractoriness.

$$*CCI = \frac{\text{(Post-transfusion count} - \text{Pre-transfusion count) } (10^3/\mu l))}{\text{No. of platelet units transfused}} \times BSA(m^2)$$

Alloimmunization to HLA antigens can be detected by serum testing for lymphocyte cytotoxicity test (LCT). One of the oldest approach to manage this refractoriness is by transfusing HLA matched platelets[18]. In the past decade, human platelet alloantigen system (HPA) was better understood at the molecular level[19,20]. HPA typing was also revolutionized by application of DNA based technology and PCR which allowed rapid mass donor typing[21]. We had personal experience with RPA matched plateletpheresis for the management of refractory cases. We used a PCR-sequence specific prime technique to type the HPA of recipient and donor platelets[22,23]. In addition simpler cheaper and faster techniques for direct donor recipient cross-matching were developed[24]. These techniques can allow the transfer of this methodology from the research laboratory to the service hospital.

Leukocyte reduction is becoming a universal strategy applied to most blood products. Countries like Great Britain, France, Austria, Norway, Portugal, Canada and most of USA have adopted leukocyte reduction policy. This approach has obvious advantages including reduction of febrile reactions, minimization of alloimmunization and leukocyte associated infections eg. CMV and HTLV. There are several approaches for leukocyte reduction, including centrifugation, pre-storage filtration, post storage filtration, cell washing and plateletpheresis. The efficiency of these different methods is variable. To prevent alloimmunization leukocyte count has to be less than 5×10^6/PC[25]. This means that some form of filtration particularly pre-storage is needed.

Storage of PC at room temperature contributes to higher rate of bacterial contamination compared with other blood products. The rate of contamination of PC varied in different studies from 0-10%[26-29]. Morrow reported in 1991 that despite careful technique in blood collection, bacterial contamination of PC occurred at a rate of 1 in 1000 but only 1 in 10,000 were clinically significant[30]. Currently available techniques for the detection of bacterial contamination include gram stain, PCR, nucleic acid detection and culture. These techniques suffer from limitations like poor sensitivity, long test time and technical complexity. There is a need to develop a practical test to detect clinically significant bacterial contamination. Burstain used urine reagent strips for this purpose and found 95% sensitivity and specificity[31].

Corash in 1989 introduced photo decontamination of PC[32]. This technique combines psoralen (AMT) with UV exposure. Psoralen works by binding to RNA or DNA. In the presence of UV light cross links are introduced thus impairing nucleic acid replication. At a wavelength greater than 340nm, platelets devoid of DNA are spared and appear to have normal survival and function[33]. On the other hand this combination is effective in killing viruses like HIV, HBV, HCV, CMV and bacteria both gram positive and negative except pseudomonas which appears to be resistant[34].

In summary the future of platelet transfusions in the Gulf countries would probably witness a shift from RDP towards more SDA especially for refractory patients. Leukocyte reduction seem to be an ultimate policy for products because of its many advantages. Photodecontamination appears to be a safe means of reducing bacterial contamination. In the face of the increasing demand on platelet transfusions strict indication criteria, cost-effective transfusion regimens and quality high yield PC are recommended. Recombinant growth factors and cord blood stem cell transplantation may shorten post-chemotherapy cytopenias, therefore reduce the overall pressure on platelet transfusion. Because refractoriness is a common complication of repeated platelet transfusions, adoption of some technique for donor-recipient matching is necessary. Issues which still need further study include tests for evaluation of platelet function, tests for detection of bacterial contamination and the development of platelet substitutes or frozen platelet products.

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