수혈 대체 치료와 환자 혈액 관리의 세계 동향

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The Global Developments in Transfusion Replacements and Patient Blood Management

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Blood transfusions were once believed to be the most potent and cost-effective method of improving patients' survival outcomes, but accumulating evidence over the past thirty years strongly suggests allogeneic transfusions as independent prognosticators of complications, prolonged hospital stay, and higher costs. A growing body of health care providers in Korea and throughout the world recognize a causal relationship between these adverse outcomes with liberal transfusion policies and call for a universal paradigm shift regarding the management of blood. Currently, the most promising contender is Patient Blood Management (PBM), which has been found to improve patient outcomes by conserving or optimizing the patient's own blood and physiologic reserves and advocating for restrictive transfusion policies. PBM incorporates evidence-based transfusion replacements to address anemia, bleeding, and blood disorders. These various methods—such as intravenous iron, erythropoiesis stimulating agents, coagulating factors, and topical hemostatic agents—are gaining recognition because of their ability to preclude the need for allogeneic transfusions while effectively managing the patient's blood. (*Korean J Blood Transfus* 2017;28:103-112)

Key words: Transfusion, Patient blood management, Transfusion replacement

Introduction

Despite evidence to the contrary, many physicians in practice today subscribe to the belief that transfusions are unreservedly beneficial, and the default

treatment in instances of abnormal hematologic findings—even when indications are not appropriate—is to transfuse. Transfusion triggers based on arbitrary indications lead to the misuse and overutilization of blood products [1], which unnecessarily places pa-

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tients at risk for complications. Studies from various countries and medical disciplines independently associated liberal transfusion practices with adverse patient outcomes, longer hospital stay, and inefficient economics [2,3]. In Korea, a nationwide study found that the annual number of transfused red blood cell units has been rising due to an increasing number of recipients, and the average number of transfused units was 5.7 and 4.3 for males and females, respectively [4]. This is alarming, considering the safety and efficacy of transfusions have been vigorously tested and largely debunked within the last several decades and that transfusion of 5 or greater units of blood was found to disproportionately escalate risk of complications [5]. Although there are many pitfalls with using blood, it can be lifesaving in instances of acute, massive bleeding in major operation or trauma. Current Korean transfusion guidelines indicate for transfusion when red blood cell levels are less than 7 g/dL.

In efforts to shift an attitude towards one that precludes transfusions, clinicians should view donated blood as a limited resource that requires judicious allocation and regard the patient's own blood as a precious resource that, when harnessed efficiently, could play a significant role in optimizing patient outcome. The increased risk of adverse outcomes associated with a transfusion should be carefully balanced against its benefits. Korea's aging population coupled with a declining donor pool is placing an ever-increasing demand on the Korean Red Cross, and reports predict chronic blood shortages in the near future unless medical practice changes significantly [6]. Continued dependence on blood can also leave medical professionals unprepared when a

shortage does occur, such as in cases of natural disasters and epidemics. On the other hand, the concept of viewing the patient's own blood as a precious resource came as a result of treating Jehovah's Witnesses who, despite their refusal of transfusions for religious purposes, recovered from acute anemia, surgery, and even life-threatening blood loss with outcomes equivalent to or better than that of situations where transfusions would have been considered critical to achieve desirable outcomes [7].

Ultimately, concerns about the safety of blood and its looming scarcity calls for a shift in attitude from supply- to a patient-centered approach in treating patients at risk of transfusion. Rather than focusing on making blood "safer-than-ever" and streamlining supply and demand, a shift in focus towards managing the patient's own blood and providing safe, evidence-based strategies that are individualized to each patient's physiology and circumstances has been gaining international attention and validation. Collectively, this has been termed Patient Blood Management (PBM) and is currently the most viable replacement for liberal transfusion policies.

Patient Blood Management (PBM)

In 2010, the World Health Organization (WHO) endorsed PBM as a worldwide trend that should be embraced by all medical communities (WHA 63.12) [8]. PBM is a multidisciplinary, individualized approach to optimize patient outcome through the systematic implementation of effective and safe blood management strategies, including the minimization or elimination of unnecessary exposure to trans-

fusions [9]. Several countries, such as Australia [10], the United States [11], and the United Kingdom [12], have already introduced nationwide PBM programs to address the various problems associated with liberal blood transfusion, and results indicate superior outcomes regarding patient health and cost-effectiveness.

Domestically, the Korean Research Society of Transfusion Alternatives initiated PBM in 2006. In 2014, the Korean Patient Blood Management (KPBM) Research Group was formed to further promote greater PBM use, and their active participation saw PBM included in the Korean Transfusion Guidelines for the first time in 2016. A PBM steering committee, called the Korean Society for Patient Blood Management, was formed in the same year to implement PBM nationwide. The Korean Society of Blood Transfusion (KSBT) supported PBM with the creation of a PBM committee in 2016. A KPBM survey showed that 70~80% of practicing surgeons supported the use of PBM and held special PBM symposia within their respective societies [13-15].

Recent, long-term studies on fully operational PBM programs worldwide have shown overall improvements in patient outcomes, reduction in health care costs, and/or increased satisfaction by medical professionals [16,17]. In 2008, the Western Australia Department of Health implemented a comprehensive, health-system-wide PBM program based on the 3-pillar structure [10]. A recent report of 4 major tertiary hospitals in Australia (605,046 patients) showed that with a mean decrease of pre-transfusion hemoglobin levels from 7.9 g/dL to 7.3 g/dL ($P < 0.001$), a 41% decrease in transfused blood products and risk-adjusted reductions in hospital mortality,

length-of-stay, hospital-acquired infections, acute myocardial infarction-stroke, and all-cause emergency readmission rates were observed [16]. Another study that analyzed health-related outcomes of a comprehensive PBM program observed reduced transfusion rates, hospital length-of-stay, and all-cause readmission rates [17]. Rates of anemia also decreased from 26% to 10%, and perioperative RBC loss decreased by 20%. Investigators concluded that a systematic approach to managing hemoglobin and RBC levels resulted in decreased transfusion rates.

In addition to health-related consequences, transfusions play a significant role in diminishing the symbolic ratio between efficient healthcare delivery and total cost [18]. Blood transfusions are one of the most common procedures performed worldwide, and adverse events that arise from transfusions are among the greatest expenditures in the health care delivery infrastructure. In a study measuring the costs of RBC transfusion, transfused patients were 30% less likely to have been discharged from the hospital at all postoperative time points, and the cost of admission could have been reduced by 40% if transfusions were avoided. A comparative study of restrictive versus liberal transfusion policies in one hospital found that acquisition costs of RBC units per 1000 patients decreased from \$283,130 to \$205,050 in a relatively short span of 4 years, with an estimated total savings of \$6.4 million [19]. These results did not include additional savings expected from total transfusion-related costs. Despite spending less per patient, hospital-wide clinical outcomes showed statistically significant improvements in mortality rates, length of stay, and readmission rates.

Transfusion Replacements in PBM

Various pharmacological and technical strategies that aim to conserve and optimize the patient's own blood form the backbone of PBM, which, in turn, deemphasizes transfusions. This "bloodless" armamentarium of therapies and maneuvers can essentially be categorized into the 3-pillar matrix of PBM [20]:

Pillar 1: Recognize and treat anemia by optimizing red blood cell mass

Pillar 2: Minimize blood loss and bleeding

Pillar 3: Harness and optimize tolerance of anemia, including compliance to restrictive transfusion policies

Specific strategies employed by PBM are listed in Table 1.

1. Intravenous iron

Iron-deficiency anemia is considered to be one of the most overlooked yet prevalent morbidities in patients with chronic diseases, and arbitrary "transfusion triggers" results in the unnecessary transfusion of patients with anemia, which places them at increased risk of preventable, transfusion-related adverse outcomes [9]. However, studies found that identifying and treating the underlying cause of anemia can effectively reverse this condition and therefore render transfusions unneeded [20]. A single, 15-minute, high dose injection of ferric carboxymaltose (FCM), a stable and lowly immunogenic intravenous iron compound, has been approved for use in numerous countries for the treatment of iron-deficiency anemia [21]. Multiple Phase III, randomized clinical trials testing FCM against diverse anemia-inducing etiolo-

gies (inflammatory bowel disease, cancer, post-partum anemia, abnormal uterine bleeding, chronic heart failure, and chronic kidney disease) support this conclusion [22], and a randomized clinical trial recently demonstrated its ability to effectively and rapidly treat postoperative acute isovolemic anemia, as well [23]. FCM is generally well-tolerated with low risk of inducing serious hypersensitivity reactions and has emerged as an important therapeutic modality in reducing the need for blood transfusions [24].

2. Erythropoiesis-stimulating agent (ESA)

ESAs stimulate bone marrow to produce red blood cells (similar to human protein erythropoietin), and their ability to minimize the need to transfuse has resulted in its regulated approval. Administration of ESAs has been approved for patients undergoing elective surgery and patients with anemia induced by chronic kidney disease, human immunodeficiency virus treatment, and chemotherapy. However, approval was not necessarily given for any other benefits, as studies evaluating ESA use demonstrated worsened overall survival, safety, and quality-of-life [25]. A more conservative use has therefore been recommended because of the adverse outcomes associated with ESAs, which has resulted in a boxed warning from the FDA that usage can increase the risk of death, myocardial infarction, venous thromboembolism, thrombosis of vascular access, tumor progression, and recurrence [26].

3. Tranexamic acid

Administration of tranexamic acid, an inhibitor of

Table 1. Pharmacologic and technical strategies of PBM

	Name	Description
Red blood cell mass optimizers	Erythropoiesis stimulating agent (ESA)	Stimulates bone marrow to make red blood cells
	Intravenous iron	Treats iron deficiency; reverses acute isovolemic anemia [21-24]
Antihemorrhagic agents	Tranexamic acid	Inhibitor of plasminogen and fibrinolysis [27-29]
	Prothrombin complex concentrate	Vitamin K-dependent blood coagulant; reverses over-anticoagulation [30]
	Fibrinogen concentrate	Used as a coagulant in patients with congenital fibrinogen deficiency [33,34]
	Recombinant factor XIIa	Stimulates thrombin activity to form hemostatic plugs [35,36]
	Aminocaproic acid; epsilon acid	Inhibitor of plasminogen activation [39,40]
	Vasopressin	Hormone drug that increases water reabsorption and retention; constricts blood vessels
	Somatostatin	Increases vascular resistance; increases platelet aggregation [41]
	Octreotide	Somatostatin analog [42]
	Desmopressin acetate (DDAVP)	Enhances platelet adherence [43]
	K-vitamin (phytomenadione)	Reverses and stabilizes over-anticoagulation [44,45]
	Topical material to control bleeding	Stabilizes bleeding through compression and coagulation [37,38]
Autologous blood salvage	-	Primary goal is to reduce/avoid allogeneic red blood cell transfusion: safety of blood increased [46]
Acute normovolemic hemodilution	-	Similar to autologous blood salvaging, except the patient's blood is diluted with colloid and/or crystalloid to maintain hemodynamic stability [47]
Artificial oxygen carriers (AOC)	-	Free of infectious agents and accepted by all blood types (efficacy to be determined) [48]

plasminogen and fibrinolysis, has been found to reduce morbidity and mortality in trauma and surgical patients by approximately a third [27]. Intravenous tranexamic acid has also been found to reduce rates of readmission and blood transfusion in perioperative settings, and topical versions can also be applied for reduction of bleeding [28]. Contraindications are few (most important are ongoing thrombosis and allergy to tranexamic acid) and there are few side effects from its use [29]. Although high doses can lead to adverse neurological events, reasons to administer high levels that can cause such damage is not substantiated by clinical trials. A dose of 1 g in adult patients reaches maximal potency, and efficacy immediately levels off at this dose. Additionally, a randomized clinical trial of over 20,000 patients showed no increase in risk of thromboembolic events after early use in trauma patients [25].

4. Coagulopathic factors

1) Prothrombin complex concentrates (PCC)

PCC, a plasma product consisting of vitamin K-dependent factors, is a blood coagulant used in patients who require rapid reversal of the international normalized ratio (INR) due to supratherapeutic INR or severe bleeding [30] and results in a clotting factor concentration of greater than twenty-five times that of human plasma [31]. The primary indication for PCC is for the urgent reversal of warfarin overdose, a vitamin-K dependent clotting factor inhibitor.

2) Fibrinogen concentrate

Fibrinogen concentrate is a virally-inactivated product designed to rapidly replace depleted plasma fibrinogen by enhancing blood clot formation and

platelet aggregation [32]. Use of fibrinogen concentrate is indicated for treatment of inherited fibrinogen (factor I) deficiency in the U.S. and Europe, but results supporting for its use in response to trauma-related coagulopathy has not been demonstrated yet [33,34].

3) Recombinant factor VIIa (rFVIIa)

rFVIIa is a bypassing agent that initiates a burst of thrombin activity through the extrinsic pathway of the coagulation cascade, resulting in a stable hemostatic plug [35]. The US FDA approved it in 1999 and 2005 for the reversal of bleeding caused by acquired and congenital factor VIII (hemophilia A) and factor IX (hemophilia B) deficiencies [36]. Indications have also expanded to include hemophilia, acquired factor VII deficiency and Glanzmann's thrombasthenia—the latter has only been approved in Europe.

5. Topical hemostatic agents to control bleeding

Major goals of surgery- or trauma-related hemorrhaging are to minimize blood loss and regain control of hemostasis without the delay seen with endogenous and systemically infused responses to bleeding. Not only do topical agents reduce the time needed to achieve hemostasis, but their usage also decreases the need for blood transfusion as bleeding can be staunched relatively quickly [37]. The use of local agents to achieve hemostasis, however, can lead to adverse events, such as mechanical injury, delayed phlogistic effects, infections, and anaphylaxis [38]. Notable topical hemostatic materials and agents include the following: oxidized cellulose hemostat for wound compression, fibrin adhesive/glue

and sealers, fibrin or platelet gels, hemostatic collagen, jelly foam/sponge, topic buffered or soaked with thrombin, vegetal origin polysaccharides, and calcium alginate

Conclusion

The long held belief that transfusions improve patient outcomes should no longer be a statement grounded in reality. Transfused patients are unnecessarily exposed to danger, and many lives have been complicated or ended by this practice. Multi-disciplinary approaches to PBM are necessary to optimize the care of patients who may need a blood transfusion, and implementation of a nationwide PBM program that incorporates evidence-based transfusion replacements can substantially update the overall landscape of health care by not only improving patient outcome through reducing transfusion rates and personalizing health care but also by raising cost-efficiency. To accomplish this, strategic support from the Ministry of Health and Welfare, Center for Disease Control, and the Korean Society of Blood Transfusion is needed to raise awareness of this issue and effectively establish PBM as a new, national standard of medical care.

요약

수혈은 한 때 환자의 생존율을 향상시키는 가장 강력하고 비용-효과적인 방법으로 생각되었지만, 지난 30년 동안 축적된 증거는 동종 수혈이 합병증의 증가, 입원 기간의 연장, 입원 비용을 증가시키는 독립적인 예후 인자임을 강력하게 시사한다. 한국 및 전세계의 의료계는 점차 이러한

바람직하지 않은 임상 결과와 자유로운 수혈 정책 사이의 인과 관계를 인식하고 혈액 관리와 관련하여 전폭적인 패러다임 전환을 요구하고 있다. 현재 수혈의 가장 유망한 경쟁자는 환자혈액 관리(Patient Blood Management, PBM)이다. 환자혈액관리는 환자 자신의 혈액과 생리적 여력을 보존하거나 최적으로 활용하도록 하며, 제한적인 수혈 정책을 지지한다. 환자혈액관리는 빈혈, 출혈과 혈액질환을 교정하기 위해 근거 중심 수혈 대체제들을 통합한다. 정맥용 철분 제제, 적혈구 조혈 자극제, 혈액 응고제와 국소 지혈제와 같은 다양한 방법들이 동종 수혈의 필요를 배제하도록 하며 환자 혈액을 효과적으로 관리하도록 한다.

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