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Transfused trauma patients have better outcomes when transfused with blood components from young donors

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A B S T R A C T

The physiology of tissue healing and aging share common pathways. Both patient age and tissue healing are crucial factors predicting outcomes in trauma patients. The presented hypothesis focuses on the concept that transfused trauma patients have better outcomes when transfused with blood components from young donors. The age of the donor of a blood transfusion could affect recovery following a major traumatic insult and help avoid postinjury immune paralysis and its associated complications. The frequent transfusion of blood components to the severely injured trauma patient provides an opportunity for the recipient to benefit from the potentially favourable effect of blood originating from young donors. Different types of evidence support the presented hypothesis including work on soluble circulating factors, research on animal parabiontic models and epidemiological studies. Theories on the role of transfusion of cells, on bone marrow and on senolytics also represent grounds to elaborate pathways to test this hypothesis. The precise molecular mechanism underlying this hypothesis is uncertain. A beneficial effect on trauma patients following transfusion of blood could be due to a positive effect of blood donated from younger donors or instead to the lack of a negative effect possibly occurring when transfusing blood from older donors. Either way, identifying this mechanism would provide a powerful tool enhance long and short term recovery after trauma.

Introduction

The complex physiology underlying tissue healing after major injury is only partially understood in its molecular mechanisms but age-related reduced healing capability is often observed in clinical practice and younger humans are known to regenerate faster. Aged critically ill trauma patients are particularly sensitive to compromised physiological responses [1]. In fact, suboptimal tissue reparation and host defence can result in septic complications [2], bone marrow failure [3], multiple organ failure (MOF) [4] and persistent inflammatory, immunosuppressed, catabolic syndrome (PICS) [5,6].

Multiple systemic changes and regional factors impair tissue healing and recovery from injury in aged physiology. Conversely, these factors play a role in the sturdiness of the physiological response and capability to recover in younger patients. While young people typically elicit a vigorous response to physical insult, elderly patients often succumb following comparatively minor injuries without evident systemic response.

Polytrauma patients suffer from severe tissue injury and compromised homeostasis and the potential iatrogenic complications associated with aggressive resuscitation [7] and multiple surgical procedures; this results invariably in a systemic inflammatory response and increased risk of organ dysfunction and failure even of uninjured organs. The acute phase of traumatic shock resuscitation is managed with timely haemorrhage control and balanced replacement of packed red blood cells (PRBC), platelets, plasma and concentrated coagulation components. Survivors of the first 24 h may spend weeks in intensive care units in a severe catabolic, hyper-inflammatory state. These patients' hospital courses are frequently compromised by organ failure and septic complications. During this complicated critical care phase, they often require additional PRBC transfusions to replenish their circulating haemoglobin concentration while their bone marrow is dysfunctional [3]. Optimal tissue healing is crucial to trauma patients to recover from their injuries. An efficient switch to anabolic metabolism and the timely transition from postinjury hyper-inflammation to adaptive immune response determines the likelihood of overcoming both the initial insult of major trauma and the dangers of the nosocomial environment.

Soluble molecules circulating in donated blood could still be effective on the recipients' physiology. Theoretically, in transfusing a patient with blood components drawn from a young donor we could be unwittingly administering a component with a therapeutic potential that goes well beyond replacing the relevant blood component (Fig. 1). The polytrauma population demands optimised physiological resources for tissue healing and overall recovery, coincidentally their care may require the administration of large amount of blood components. These

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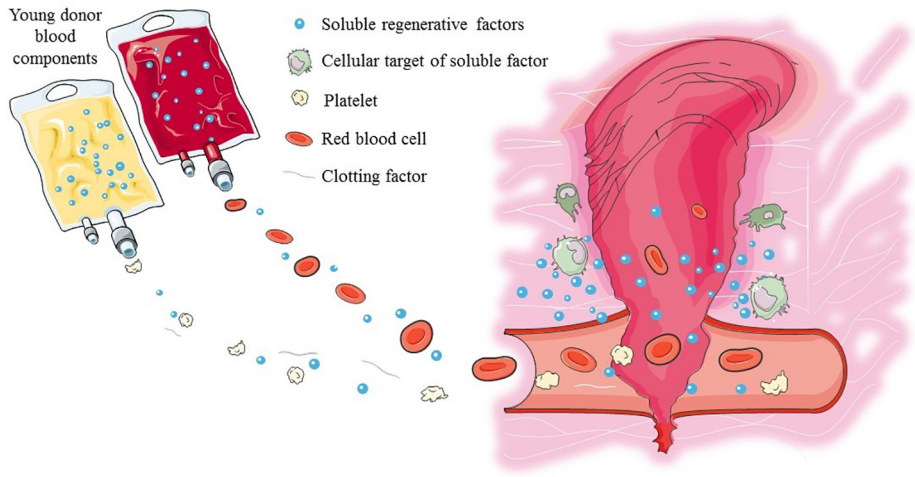

Fig. 1.

two facts provide the potentially elegant solution of young donors' blood components being administered and improving outcomes when blood components are already required as standard of care.

Hypothesis

Idea evolution

Transfusion of blood and blood components is literally vital to severely injured haemorrhaging patients and trauma is one of the most common and unquestioned indications for acute transfusion. Different rationales and scientific evidence underpinned the alternation of restrictive versus liberal blood component transfusion policies over time. Meanwhile, blood component transfusion has been identified as independent predictor of complications such as transfusion related acute lung injury (TRALI) [8], acute respiratory distress syndrome (ARDS) [9] and postinjury MOF [10]. The recent trend has been away from crystalloid and isolated PRBC based trauma resuscitation [11,12] toward more product balanced "haemostatic" resuscitation [13] with minimised risk to iatrogenic coagulopathy, improved survival and increased use of blood components [14,15].

Various transfusion related strategies have been employed to affect recipients' outcomes and evidence continues to accumulate around these strategies; for example leukoreduction and storage age. Leukocytes have been associated with various adverse consequences of blood transfusions through transfusion-related immunomodulation phenomenon [16], however no clear high quality evidence is available to draw a conclusion regarding routine use of leukoreduction for prevention of TRALI [17]. Regarding storage age, many years of discussion in the literature was followed by lack of correlation in which no 90-day mortality benefit was demonstrated [18]. Blood donor age has only more recently become the focus of investigation. No evidence is available to date correlating blood donor age and recipient trauma patients' outcome.

Importance of idea

The importance of this idea is that there might be a hidden but uniformly available opportunity to decrease postinjury complications and death related to delayed recovery and immunological paralysis in trauma patients. Additionally, improved outcomes would limit the associated cost of hospital care due to MOF, sepsis and PICS. Minimising generalised weakness and fatigue, chronic bone marrow failure and sarcopenia seen in trauma patients with impaired healing will help these patients to return to their pre-injury activity and functional status. If the hypothesis was verified it would be possible to minimise the potential harmful effects on recovery from the suboptimal donor-aged components.

Trauma represents the second most common indication for massive transfusion [19]. A review from a single trauma centre screened patients admitted for trauma finding that 8% of all admitted patients received PRBC, 3% were given 10 units during their stay, and 1.7% received 10 units of blood in the first 24 h after admission [20]. Classically, massive transfusion has been considered as 10 or more units of PRBC given within 24 h. More recently, some authors use the threshold of 10 units in 6 h to define massive transfusion [21,22].

Whole blood is not widely used in modern civilian clinical practice and blood components are normally processed before being available for usage. It is reasonable to presume that the processing of whole blood into ready-to-use components, for example RPBC, plasma, cryoprecipitate and platelets, could affect the presence of soluble factors in the transfused components. Considering the large volumes of blood components received by major trauma patients and the potential for active soluble factors to be contained in blood components from young donors the effect of blood donor age on trauma recipients should be investigated. It is clear that severely traumatised patients represent a valuable cohort of patients on whom to test our hypothesis because they frequently receive a large volume of blood components at the time of their initial resuscitation and regular top ups throughout the later acute phase of their hospital admission.

Discussion of hypothesis

Evidence is available to provide support to our hypothesis including work on soluble circulating factors, research on animal parabiontic models and epidemiological research. For completeness, additional studies on cell transfusion theory, on the role of bone marrow, and on senolytics will be briefly presented. The following studies explore the molecular mechanisms underlying the hypothesised beneficial effect of young blood.

Supporting evidence – soluble factors

The enormous amount of proteins circulating in the bloodstream, their metamorphic features, and our partial understanding of their wide-ranging interactions [23] make the identification of molecules potentially responsible for making blood a powerful drug a difficult challenge. Identifying these circulating factors and proving that their concentration or function changes in serum with age would help explain any correlation found between donor age and recipients'

outcomes. Demonstrating the persistence and viability of such factors through the process of manufacturing blood components, freezing, transportation and storage would also clarify an observed effect.

Two studies have been conducted in humans investigating the potential effects of plasma transfusions from young donors. Results from these studies have not been formally published to date but some information including methodology is available through the registry maintained by the United States National Institutes of Health. The Plasma for Alzheimer Symptom Amelioration Study [24] enrolled 18 individuals aged between 50 and 90 to investigate on the possibility that patients with Alzheimer's disease experience cognitive improvement when transfused with plasma from healthy younger donors. This single-arm, interventional study enrolled patients affected with Alzheimer's to receive one unit of plasma from young, male donors, aged 30 years or younger, once weekly for 4 weeks. Safety and tolerability were the primary outcomes. Cognitive scales, normally used to measure cognitive and functional Alzheimer-related impairment, were chosen to measure secondary outcomes. Colloquial dissemination of results claimed safety and a minor, but detectable, performance improvement against some of the selected assessment scales. Another study worth noting is the recently concluded Young Donor Plasma Transfusion and Age-Related Biomarkers study [25] which evaluated the beneficial effects of infusions of plasma from young donors by measuring circulating levels of blood biomarkers. A single group of 200 participants paid to receive an infusion of plasma derived from a young donor aged between 16 and 25 years. A large panel of biomarkers were measured in the participants' blood before and 1 month after transfusion. The only criteria for enrolment was being at least 35 years of age; and the study did not have a control arm. Interim results have been presented claiming reduced amyloid and carcinoembryonic antigen levels. The significance of these findings is yet to be clarified.

Plasma Growth and Differentiation Factor 11 (GDF-11) is a cytokine member of the Transforming Growth Factor-Beta superfamily [26], the concentration of which has been found to be age-dependent [27]. This molecule has often been considered to be a protein holding a rejuvenating effect, nevertheless scientific findings have been contradictory [23]. GDF-11 is involved in embryonic development, erythropoiesis, the pathophysiology of aging, cardiovascular disease, diabetes mellitus and cancer. Heterogeneous findings have been reported regarding its role in aging, cardiovascular disease, diabetes mellitus, osteogenesis, skeletal muscle development, and neurogenesis. GDF-11 was found to reverse symptoms of heart failure in older mice when tested in animal models [28] demonstrating cardiac hypertrophy regression and molecular remodelling accompanying a reduction in cardiomyocyte size. It has also been found to reverse age-related stem-cell dysfunction in brain [29] and muscle tissue [30]. On the contrary other authors reported a strong inhibitory effect of GDF-11 on muscle regeneration [31]. Lastly, GDF-11 has been found to inhibit erythroid maturation [32] and has been implicated in ineffective erythropoiesis in β-thalassemia [33].

Numerous soluble factors have been studied in an attempt to identify a circulating protein responsible for the beneficial effect of young blood. Beta-2-Macroglobulin [34], cyclic adenosine mono phosphate response element-binding protein [35], methylcytosine dioxygenase 2 [36] and vascular cell adhesion molecule-1 [37–39] represent some examples. To date, the results on these are inconclusive.

Supporting evidence – animal parabiontic model

Parabiosis is an old animal experimental model where two animals are surgically joined together to create a shared circulation [40]. This technique was recently brought back into focus following a seminal publication from a research group with a focus in aging and rejuvenation [41]. Heterochronic parabiosis is created between two animals of different ages. Several studies of heterochronic parabiontic rodent pairs showed an effect on multiple organs following exposure to a shared circulation [42]. A shared circulation changes the milieu in which recipient animals' cells live and this seems to actively influence cell function. This is likely the result of soluble factors that travel through the surgical connection from one animal to the other. It seems logical to presume that a young and an old organism sharing a circulation can reciprocally affect each other. Based on tests and observations used to measure changes in animals following heterochronic parabiosis, authors have concluded that factors originating from young animals can be beneficial; on the other hand, circulating factors originating from old individuals could have a detrimental effect on the younger animal. In others words, the former being potentially rejuvenating [41], the latter promoting aging [38]. This idea has been further expanded by proving similar effects without needing to permanently share a circulation but simply by administering young plasma. In their experiments, Villeda et al. repeatedly injected plasma from young mice into old mice demonstrating an increase in memory function [35,43].

Young blood has proven regenerative properties on various organs and through multiple pathways in animal studies. Effects have been observed in the liver, and in muscles [30,41]. In the lustrum 2010–2015, effects were observed on heart [28], pancreas [44], bones [45], the nervous system [29,35,38] and also hair follicles [46]. Liver regenerative capacity has been proved to decline with age as a result of reduced responsiveness of tissue specific resident stem cells. Conboy showed young blood was able to reverse age-related decline in progenitor hepatocytes of old rodents. In addition, tissue specific hepatic stem progenitors from aged animals in heterochronic pairs have shown increased proliferation. This correlated with reduced levels of cEBP-α-Brm complex, a specific complex associated with age related decline in hepatocyte proliferation. Furthermore, efficacy of muscle regeneration was analysed by the same research team. Rodents were paired in a heterochronic and isochronic fashion and after 5 weeks of parabiosis some muscular injuries were provoked. Enhanced muscular tissue regeneration was observed in old partners of heterochronic pairs. Loffredo's group reported on effects of heterochronic parabiosis on the heart. After 4 weeks, a reduction in cardiomyocyte molecular remodelling and size was noted. There was also regression of cardiac hypertrophy. This has been hypothesised to be related to exposure to younger blood. Age-related reduction in pancreatic β-cell proliferation likely plays a role in age related prevalence of type 2 diabetes and is therefore clinically very important. Salpeter demonstrated that β-cells proliferate more when exposed to a young mouse's circulating factors and concluded that β-cell replicative decline in the pancreas of old mice is related to the influence of systemic circulating molecules. Bath et al. investigated the mechanism by which circulating and mesenchymal stem cell-related factors influence age related changes in bone repair. Beta-catenin seems to be involved in mediating this process, with bone healing seemingly improved in old mice from heterochronic pairs when compared to that observed in aged mice. Neurogenic rejuvenation aroused significant interest with multiple authors contributing to this research topic. Old rats subject to heterochronic parabiosis showed increased neurogenesis and neurovascular remodelling. The role of the systemic milieu has proved to influence cognitive function. Lastly, parabiosis has been used to assess aged related changes in hair follicle stem cell function. A mild improvement in colony-forming efficiency has been found, however some intrinsic tissue factors also play an important role in age-related hair follicle decline.

Supporting evidence – epidemiological studies

In the recent past, a number of studies tried to identify a link between donor age and unstratified recipient's outcomes, nevertheless findings have been equivocal.

Vasan et al. conducted a large retrospective epidemiological study based on information collected through a population health database and a Scandinavian donation and transfusions database [47]. Patients

received fresh frozen plasma and PRBC over a 17-year time frame. Large numbers were analysed, with 45.664 plasma recipients and 136.639 PRBC recipients. No association between donor age and survival of the transfused patient was found at 30 days nor 1 year. Exceptions to the overall pattern were represented by reduced 30-day mortality for cerebrovascular patients receiving fresh frozen plasma from donors over 50-year-old and increased 1-year mortality for patients receiving fresh frozen plasma from donors over 50 years of age. Another recent study from Chasse et al. [48] analysed information collected from a blood collection agency and from clinical databases at 4 academic institutions to evaluate a possible link between the age and sex of the blood donor and recipient survival. The size of the analysed sample was remarkable; a total of 30,503 recipients, 187,960 PRBC units and 80,755 donors were considered. Results were surprising, demonstrating an 8% increased mortality for recipients receiving PRBC from females. Furthermore, an 8% and 6% increased mortality was noted when patients received blood from 17 to 20-year-old donors and 20 to 30-year-old donors respectively (compared to donors aged between 40 and 50 years of age). Edgren's group [49] subsequently replicated the study from Chasse et al. with adjusted statistical analysis methods to accommodate nonlinearity. It was concluded that an association between donor age and sex and patient survival was no longer proven and, therefore, not to be considered in blood allocation in clinical practice. The authors believe that the previously reported findings could be explained by residual confounding [50]. Lastly, a retrospective cohort study was published by Guinn et al. [51] on patients undergoing coronary artery bypass grafting who received plasma during or after surgery. Transfused plasma units were divided into tertiles according to donor age and correlation was sought with outcomes including mortality and length of hospital stay. With 1306 patients receiving plasma perioperatively, transfusion of a greater number of plasma units was associated with patient mortality, donor age was not. No difference in mortality was found between tertiles and all outcomes were independent of plasma donor age.

Large epidemiological studies run interrogating databases have the potential to overcome the common pitfalls of clinical research but are prone to other bias. Such studies incur a high risk of being affected by many confounding factors intrinsic to large human populations who receive blood components for different indications and with different regimens [52,53]. Studies on more focused populations are more likely to produce more meaningful outcomes. Severely injured trauma patients have all characteristics to provide a suitable subgroup for this analysis. This will be true especially if a dose effect is involved in the hypothesised underlying molecular mechanism. Because such subgroup does receive larger amounts of blood components over a shorter period of time a correlation to a clinical outcome would be more evident.

Supporting evidence – additional studies: cell transfusion theory, bone marrow and senolytics

The process of separating donated blood into blood components varies both geographically and over time with emerging available technology and evidence. Such differences make it difficult to come to homogeneous conclusions regarding soluble factors contained within donors' blood. In other words, the presence of soluble factors originating from the donor and potentially exerting an effect on the recipient could be seen as questionable. Blood components are not the only way blood can be transferred from one individual to another. Whole blood was widely used before technology allowed for blood processing and storage and continues to be used in the military in recent years [54]. Also, it is recently regaining popularity in the setting of civilian trauma [55]. Whole blood represents an interesting fluid with regards to the discussed hypothesis. The possible role of a cell transfusion effect and stem cells in particular attracts the interest of researchers when considering the number and variety of circulating cells. Two authors have demonstrated the presence of adult stem cells circulating in mice blood [56,57]. Ruckh et al. demonstrated how rejuvenation of an aging central nervous system in mice requires monocytes and other factors from a young parabiontic partner [58]. Furthermore, it has been demonstrated that mobilisation and subsequent homing of circulating stem cells is directed by chemokines [59]. Interestingly, aging adult stem cells lose their regenerative capacity in different tissues [60]. It could, therefore, be argued that in a parabiontic pair, cytokines from the old mice attract young efficient stem cells from the young to the old mouse, thus explaining the mysterious rejuvenating effect.

The bone morrow is home to all haematopoietic cells, including both myeloid and lymphoid lineages originating from pluripotent stem cells. It seems logical to presume that bone marrow could nest the molecules or cells underlying the favourable effects of young blood. Hematopoietic stem cells lose their proliferative capability with age [61] the lymphoid line production declines with age, however myeloid production is maintained over time [62]. The previously demonstrated concept that allogenic blood transfusion induces immunomodulation and affects erythropoiesis [63] could be related to blood donor age dependent factors in the trauma patient population. Nevertheless, with leukoreduction being widely adopted across blood authorities [64] despite a lack of definitive evidence for benefit or harm [17], this is unlikely to have a significant physiologic impact. Allogenic PRBC are thought to suppress T-cell receptors through an arginase dependent mechanism [65]. Arginase production has been proven to decrease with age [66]. Based on this evidence, Loftus et al. hypothesised that PRBC donated from older subjects may be less immunosuppressive compared to those from young donors. Their analysis, however revealed a possible association between blood from older donors and an increased risk of nosocomial infections among trauma patients receiving allogenic blood [67]. Moreover, Livingston et al. focused on the bone marrow as potential organ involved in post-traumatic MOF. They demonstrated bone marrow failure following severe injury. Increased release of myeloid and erythroid progenitors into the blood has also been demonstrated in association with decreased resident cell growth in the bone marrow. A key role for mesenteric lymph in haemopoietic failure following haemorrhagic shock has been demonstrated together with evidence of mobilisation of progenitor cells to the site of injury in rats [68,69].

The importance of tissue healing for trauma patients and of its age-related variability has been discussed. Interestingly, evidence derived from a seemingly disconnected field has shown healing to be impaired by immune suppression. Wound healing is notoriously delayed by the use of mammalian target of rapamycin inhibitors in kidney transplantation [70]. A better understanding of a shared sustaining pathophysiology could lead to interesting future developments. Mammalian target of rapamycin is the core component of an enzyme that regulates cell growth, proliferation, motility, survival, protein synthesis, autophagy and transcription [71,72]. Its activation in genetically defined mouse models has been proven to accelerate wound healing [73]. Rapamycin was originally developed to prevent surgical implant rejection and is now also part of a class of drugs used to delay aging: senolytics [74]. These are agents that selectively induce apoptosis of senescent cells. It is thought that senescence is a defensive response that prevents a cell from becoming tumorous, nevertheless senescent cells secrete inflammatory mediators that promote aging and hamper healing. Studies in this field are still preliminary and, to date, only animal models have only been tested [75].

Hypothesis testing

Retrospective analysis will represent the initial research approach. Demographic data from blood component donors will be matched with trauma patients' outcomes. Patient factors, injury severity and pattern, shock and physiological severity, and treatment factors will be matched as confounding variables to reliably assess outcomes. A stepped approach will be used; a small cohort of patients will be analysed as a pilot group to assist in the process of preliminary testing the presented

hypothesis. A larger cohort of patients will then be included, still in a retrospective fashion, upon validation of pilot data. Once retrospectively validated, hypothesis validity will be further challenged in greater detail by prospective multicentre research. Potential international collaboration will be considered. MOF will be used as outcome measure as it can reliably be defined prospectively and is a meaningful composite outcome to gauge the effect of transfusions in major trauma patients. Laboratory based basic science research on clinical samples will target the best supposed molecular pathway underlying this hypothesis, as guided by preliminary and exploratory research. Findings are expected to change transfusion practice to more targeted donor selection and ultimately improve major trauma patients' clinical outcomes due to enhanced potential to recovery.

Conclusion

The presented evidence represents a solid ground for the hypothesis to be tested. Not much certainty is available around the molecular mechanism underlying the hypothesised beneficial effect of young blood. Nevertheless, increasing interest is emerging in the current literature around potential consequences of the donor age on blood recipients' outcomes; answers are yet to be given. Considering the wide and heterogeneous range of theories to be explored, tested and confirmed it will be difficult to precisely illustrate the mechanism that could explain the beneficial effect of young blood. The importance of tissue healing in the recovery from an injury makes trauma patients an invaluable cohort of patients to test this hypothesis. Trauma patients often receive blood products regardless; no additional intervention is needed to test the hypothesis apart from the dedicated donor matching. If the hypothesis is refuted, the value of this work would be in definitively answering current conjecture to allow for a shift of further research efforts towards a more predictive focus. Otherwise, subsequent translational research would follow, seeking to demonstrate the entire process from the identification of the beneficial transfused entity to the favourable recipient outcome. If confirmed, implications would likely extend beyond the trauma field. As discussed above regarding epidemiological studies, extreme caution must be used before coming to rushed conclusions on this topic; there is potential for major repercussions on practices of fundamental importance, such as blood donation and its regulation. Lastly, because heterogeneous motives drive the research push for highly attractive topics such as "rejuvenation", it is important to underline that the goal of unveiling such a powerful therapeutic potential is to widen the options available when caring for injured patients.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

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