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A national common massive transfusion protocol (MTP) is a feasible and advantageous option for centralized blood services and hospitals

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Background A common national MTP was jointly implemented in 2011 by the national blood service (Blood Services Group) and seven participating acute hospitals to provide rapid access to transfusion support for massively haemorrhaging patients treated in all acute care hospitals.

Methods Through a systematic clinical workflow, blood components are transfused in a ratio of 1:1:1 (pRBC: whole blood-derived platelets: FFP), together with cryoprecipitate for fibrinogen replacement. The composition of components for the MTP is fixed, although operational aspects of the MTP can be adapted by individual hospitals to suit local hospital workflow. The MTP could be activated in support of any patient with critical bleeding and at risk of massive transfusion, including trauma and non-trauma general medical, surgical and obstetric patients.

Results There were 434 activations of the MTP from October 2011 to October 2013. Thirty-nine per cent were for trauma patients, and 30% were for surgical patients with heavy intra-operative bleeding, with 25% and 6% for patients with gastrointestinal bleeding and peri-partum haemorrhage, respectively. Several hospitals reported reduction in mean time between request and arrival of blood. Mean transfusion ratio achieved was one red cell unit: 0·8 FFP units: 0·8 whole blood-derived platelet units: 0·4 units of cryoprecipitate. Although cryoprecipitate usage more than doubled after introduction of MTP, there was no significant rise in overall red cells, platelet and FFP usage following implementation.

Conclusion This successful collaboration shows that shared transfusion protocols are feasible and potentially advantageous for hospitals sharing a central blood provider.

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Introduction

Modern massive transfusion protocols (MTP) use a systematic clinical workflow to reduce delay in delivery and

transfusion of blood components to patients with haemorrhagic shock from severe trauma or unsecured surgical bleeding [1–3].

Protocols that incorporate upfront transfusion of haemostatic blood components in an increased ratio of plasma and platelets to red blood cells have been widely adopted as best practice in improving outcome in trauma and reducing complications from severe injury, based on retrospective evidence from literature between 2005 and 2012 involving military and civilian trauma bleeding [4–14]. However, the early retrospective studies supporting higher plasma and platelet to red cell transfusion were vulnerable to selection bias, especially to 'survival bias', in which plasma and platelet transfusions were more likely to be transfused to surviving patients who had more time and opportunity to receive increased transfusion volumes [12, 15–21].

Clinical efficacy of increased plasma and platelet to red cell transfusion ratio required the stronger evidence of large prospective randomized controlled trials to firmly establish the survival benefit of early pre-emptive transfusion of haemostatic blood components and determine optimal transfusion ratios for blood components. This need for prospective randomized was partially addressed by recent prospective trials [22–24] evaluating both the safety and efficacy of liberal plasma and platelet transfusions in massively bleeding trauma patients, in particular the PROMMTT Trial (PRospective, Observational, Multicentre Major Trauma Transfusion Study) and the PROPPR Study (Prospective Randomized Optimum Platelet and Plasma Ratio by the Resuscitation Outcomes Consortium).

The PROMMTT study, a large prospective, multicentre observational study of trauma transfusion practices across ten major civilian trauma centres, found patients with plasma to red cell transfusion ratios of less than 1:2 were 3–4 times more likely to die than patients with ratios of 1:1 or higher in the first 6 h; the authors attempted to eliminate survivorship bias and catch-up transfusion bias by excluding patients who did not survive long enough to receive at least three blood product units (including one unit of RBCs), as well as through stratifying all patients into three groups by time interval; the inclusion of time-dependent covariates helped show an association between early infusion of increased plasma/platelet to red cell transfusion ratios and decreased mortality in the first 24 h [22]. In the PROPPR study, Holcomb and colleagues compared the effectiveness of using plasma, platelets and red blood cells in a 1:1:1 ratio vs. a 1:1:2 ratio [23]. Patients with severe trauma and major bleeding in multiple centres were randomized to early administration of plasma, platelets and red blood cells in either a 1:1:1 ratio or a 1:1:2 ratio. Although the authors concluded there was no significant difference in mortality at 24 h or at 30 days between the two groups, more patients in the 1:1:1 group achieved haemostasis and fewer experienced death due to exsanguination by 24 h. There were also no differences in rates of transfusion-related complications, sepsis, thromboembolism and multi-organ failure between the two groups despite an increased use of plasma and platelets transfused in the 1:1:1 group. Given the lower percentage of deaths from exsanguination and no differences in safety, the authors recommend a 1:1:1 transfusion protocol whilst patients are actively bleeding, till haemorrhage was effectively controlled. The data from the PROMMT and PROPPR studies support use of transfusion regimens with increased plasma and platelet in massively bleeding trauma patients, but additional prospective randomized evidence would help to establish the use of a precise high plasma: RBC and platelet: RBC ratio for trauma resuscitation [21].

Whilst there is some evidence of clinical benefit in using massive transfusion protocols with increased plasma and platelets in trauma casualties with penetrating injuries, the benefit in massively bleeding blunt trauma patients is less clear. However, patients with blunt injuries were well represented in both the PROMMT and PROPPR studies and also seemed to benefit from the higher transfusion ratios. In addition, Dente and colleagues evaluated MTP for civilian trauma and reported significantly lower 24-h and 30-day mortality for massive blunt trauma patients in the MTP cohort than a control cohort with similar injury severity scores [25].

Supportive haemostatic resuscitation of critically bleeding patients with expeditious blood support organized in a well-defined protocol is becoming clinical best practice, if not indeed standard of care, around the world [26–30]. Blood Services Group (BSG), Singapore's national blood service, initiated an effort to develop and implement a national massive transfusion protocol (MTP) in seven acute care public hospitals in 2011. We report our experience in implementing a common national MTP in Singapore, as well as discuss the benefits and challenges involved.

Background

Singapore is a small island nation with a geographical area of 716·1 km^2 and 5·3124 million residents [31]. The Island is well connected by a dense network of roads and expressways [32].

As of 2014, there are seven acute care public hospitals across Singapore providing the majority of acute trauma and inpatient services [33]. Hospitals are supported by a national blood service operated by Blood Services Group (BSG) of Health Sciences Authority, Singapore, which supplies at least 97% of all the nation's blood product requirements.

By early 2011, the majority of these acute care hospitals had either already introduced or were actively developing independent hospital transfusion protocols for treating massively bleeding patients within their own institutions. A number of these protocols were small scale collaborations with BSG started between 2007 and 2011. These protocols were targeted at small subsets of bleeding patients such as obstetric patients, with no common standards for use of blood products.

Such disparate practices at that time evidently created a number of issues limiting the effectiveness of the MTP protocols. Firstly, protocols crafted independently by hospitals were solely dependent on routine blood stocks maintained at the respective hospital. This may fluctuate depending on the intraday usage with the risk of rapid exhaustion of products when an MTP was activated. Urgent resupply of blood products from BSG can take up to 45 min in heavy traffic as the furthest hospital is 23 km away from our blood centre. Secondly, the components of the blood pack in the various MTP were not uniformed and created unnecessary confusion and inefficiencies when BSG attempted to support and supply these hospitals. Thirdly, it was difficult to audit the outcomes of the different MTPs, given the lack of consistency in the protocols used at different hospitals.

It therefore became obvious that BSG and acute care hospitals needed to jointly develop a national MTP protocol which could be easily supported and applied uniformly across all institutions.

Methods

Development of Singapore's National MTP Programme

In late 2010, the BSG invited participation of the various parties involved in developing an MTP from the seven hospitals and convened its first workgroup meeting in March 2011. The participants represented their respective hospitals and were drawn from the following disciplines.

(1) Trauma surgeons
(2) Anaesthetists
(3) Paediatric intensivists
(4) Obstetricians and gynaecologists
(5) Haematologists
(6) Transfusion specialists
(7) Blood bank managers

A number of these participants sat in their respective hospital's blood transfusion committees. The workgroup was chaired by representation from BSG.

The defined goals of this workgroup were as follows:

(1) Formulate a national MTP for Singapore based on current best practices.
(2) Establish a workflow for seamless supply of blood components needed to implement the MTP.
(3) Construct a framework for continuous audits of outcomes.

This national MTP would supersede existing local hospital transfusion protocols for massively bleeding patients and promote homogeneous transfusion practice in the care of massively bleeding patients. The ultimate aim was to provide adult patients treated for bleeding emergencies in acute care institutions access to early and appropriate transfusion support. A national MTP also simplifies the resupply of blood products by BSG and the planning of national blood requirement. The target would be a well-organized MTP protocol that provides early, proactive transfusion support in each major hospital, within the supply framework and logistical capability of the national blood supply system.

Designing the national MTP

The workgroup started by comprehensively reviewing the current literature on management of bleeding patients requiring massive transfusion and discussed prevailing controversies. Following extensive deliberation, the work group came to a consensus that the national protocol should contain the following core features:

(1) Early transfusion of packed RBC and haemostatic blood products (FFP, platelets and cryoprecipitate), following the schedule of the protocol workflow (Fig. 1), without the need to wait for investigation results to guide transfusion [34].
(2) Transfusing blood components at a low red cell to FFP/platelet ratio (Approximating to 1:1:1) [35, 36].
(3) A common MTP transfusion protocol applied on a 'hospitalwide' basis to both trauma and non-trauma bleeders; all patients with severe bleeding and considered at risk of massive transfusion would have priority access to urgent blood support delivered through this protocol [28–30, 34, 37–40].
(4) Recommend the adoption of a validated scoring system in assessing trauma patients for massive bleeding risk to assist in early and objective activation of the MTP. Using clinical judgment alone to decide on MTP activation could be challenging, time-consuming and subjected to inconsistencies.

The Assessment of Blood Consumption Score (ABC Score) is specifically recommended as the validated predictive scoring system for use in assessing bleeding trauma patients and involves four parameters (Table 1). There is the advantage of easy score calculation at bedside since weighted scoring parameters are not used [41, 42]. However, the ABC score is limited to use in trauma-related bleeding; it is not designed nor validated

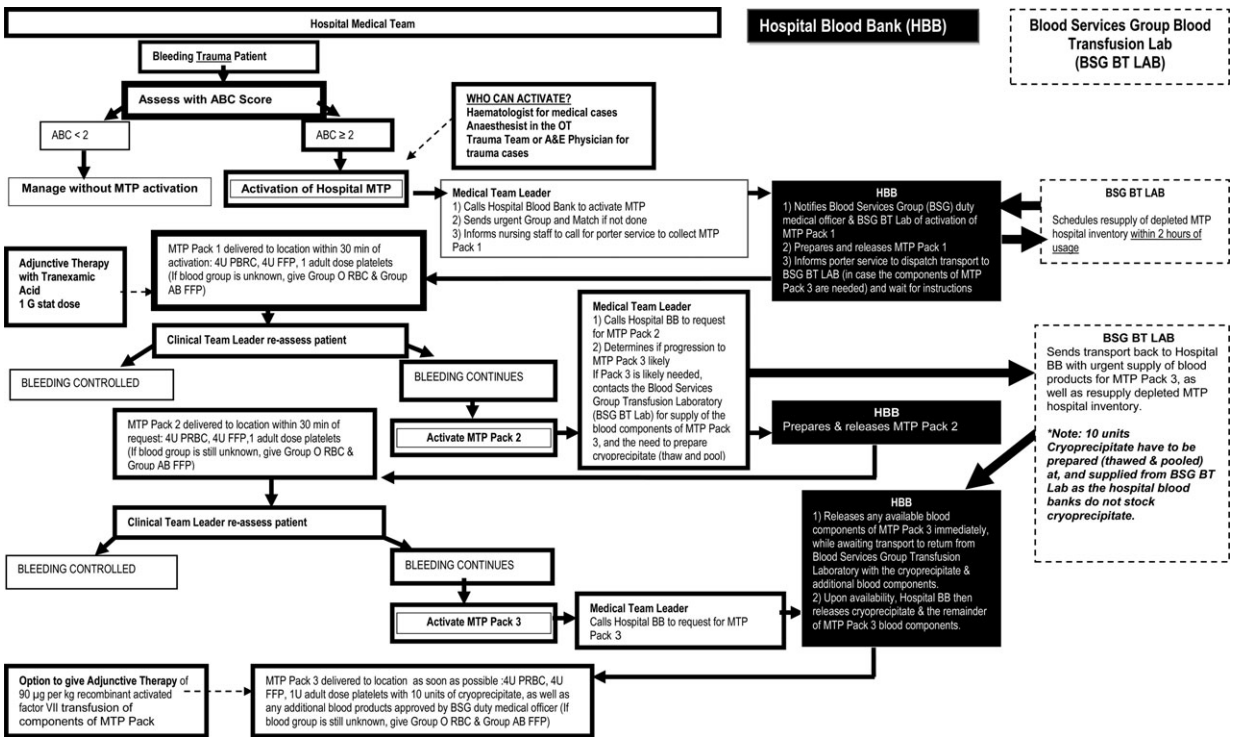

Fig. 1 Flow chart for MTP in trauma patients with critical bleeding (Initial protocol during introduction in Oct 2011).

Table 1 ABC Score for bedside evaluation of trauma patients with significant bleeding (Applicable to trauma patients only)

The ABC Score is done at the bedside of the acutely injured trauma patient early in the assessment phase using four dichotomous, non-weighted components:
. Penetrating mechanism (0 = no, 1 = yes)
. ED systolic BP of 90 mmHg or less (0 = no, 1 = yes)
. ED HR of 120 bpm or greater (0 = no, 1 = yes)
. Positive findings on focused assessment with sonography in trauma or FAST (0 = no, 1 = yes)
ABC Score of ≥2 prompts MTP activation.

for non-trauma-related bleeding, including surgical and obstetric massive bleeding.

There is no available validated predictive scoring system to objectively evaluate massive bleeding risk and guide MTP activation decision-making in patients with non-trauma bleeding in current literature. Hence, the decision for MTP activation in cases of non-trauma bleeding (major obstetric, gastrointestinal or surgical bleeding) must be made on-site by the senior clinician in attendance, based on clinical assessment of hemodynamic stability [29, 43, 44], observation of ongoing bleeding (example: observed blood loss exceeds 150 ml/min) or estimated blood loss (example: from blood-soaked swaps and linen), supplemented by laboratory parameters and results from point-of-care coagulation tests such as visco-elastic haemostatic assays if available [45, 46].

(5) Storing sufficient MTP blood components (red cells, FFP, platelets and prepooled cryoprecipitate) to maintain a dedicated stand-by inventory at all participating hospital blood banks.
(6) Incorporate use of antifibrinolytic agents into the protocol since evidence from the large CRASH-2 trial strongly suggested a survival benefit [47].
(7) A return to a restrictive transfusion strategy once haemorrhage is effectively controlled (to minimize unnecessary exposure to blood, especially plasma).

Extending the scope of patients covered by the MTP

The MTP workgroup reviewed the literature on the practice, evidence and advantages/disadvantages of adopting a general 'hospitalwide' MTP vs. applying an MTP restricted to only trauma casualties. A 'hospitalwide' MTP with a standardized component transfusion ratio and applied to all trauma, surgical and medical patients with critical bleeding is practiced by many institutions worldwide [37, 48, 49], although there is currently a lack of evidence of clinical benefit in non-trauma bleeding.

Despite the importance of transfusion support in patients with non-trauma severe haemorrhage, there is little data to guide transfusion practice, especially with regards to component transfusion ratios; several centres adopt trauma-type MTP protocols with red cell to plasma ratios ranging from 1·5:1 to 1:1 for these types of 'hospitalwide' MTPs that served both trauma and non-trauma bleeding patients [37–39, 48] since specific MTP protocols tailored to non-trauma patients are not available.

A few institutions with such 'hospitalwide' MTP applied to trauma and non-trauma patients with severe haemorrhage experienced little blood wastage with such programmes [38–40, 50], with one institution reporting no change in their blood product use after successful implementation of a hospitalwide MTP treating both trauma and non-trauma bleeders [38].

With regards to MTP applied to obstetric bleeding, one large retrospective study found that faster delivery of blood components and reduced wastage of blood components with the introduction of obstetric MTP with increased plasma and platelet transfusion [51]. Other published small case series studies described their institution's management of major obstetric bleeding after implementation of such MTPs [52, 53].

Australia and the United Kingdom have national recommendations on the use of massive blood loss protocols that focus on early recognition of major blood loss and urgent provision of blood components across a wide range of life-threatening bleeding scenarios, including obstetric, surgical and gastrointestinal bleeding [29, 30]. The Australian National Blood Authority recommends MTP activation in both trauma and non-trauma patients assessed to have 'critical bleeding', which defined as clinically substantial bleeding deemed to be life-threatening and likely to result in the need for massive transfusion and/or bleeding in a critical organ with resultant patient morbidity or mortality [29].

Since the intent of drawing up a national MTP was to organize expeditious blood support for all patients with substantial ongoing bleeding considered potentially life-threatening and likely to result in massive transfusion, the workgroup unanimously decided against a prescriptive MTP restricted to bleeding trauma patients. The MTP would cover any patient with ongoing heavy bleeding who is assessed to be at risk of ongoing exsanguination. This would include trauma patients, with either blunt and/or penetrating injuries, surgical patients, obstetric patients with serious antepartum or postpartum bleed and medical patients with gastrointestinal tract bleeding.

Blood support through use of a standardized protocol would facilitate quicker and less variable blood component support to all patients with critical bleeding. This is clinically desirable since there is association between improved outcome and expeditious, aggressive blood support, with or without increased plasma and platelet transfusion support [9, 26–28].

Composition of the 'blood packs'

Blood support in our massive transfusion protocol follows a blood transfusion ratio of 1:1:1 for RBC: platelets: FFP. Blood components are issued as MTP 'packs', each pack comprising of red cells, platelets and FFP (Table 2). A stat bolus intravenous dose of tranexamic acid 1 g is given upon commencement of the MTP, followed by an infusion of 1 g 6–8 hourly. The use of recombinant-activated factor VII (90 μg/kg) as adjunctive therapy can be considered with MTP 3. MTP transfusion support should continue till haemostasis is secured and coagulopathy corrected.

Fibrinogen replacement

Early fibrinogen replacement is critical in both trauma and non-trauma-related massive bleeding, low fibrinogen levels being associated with higher mortality in massive trauma bleeding [54–56].

Fibrinogen replacement, in the form of cryoprecipitate, is included in the MTP protocol (Fig. 1); this can be supplemented with additional transfusions of cryoprecipitate if serum fibrinogen is <1 g/dl. Each cryoprecipitate dose is set at 10 units, based on one adult dose of cryoprecipitate, since the optimal dose in severe trauma haemorrhage is still not firmly established [56, 57]. The cryoprecipitate was placed in the third MTP transfusion pack during the original launch version of our MTP protocol (Table 2) because the hospital blood banks did not have their own stock of cryoprecipitate units on-site during initial introduction of the MTP in October 2011. The intentional scheduling of cryoprecipitate in Pack 3 reflected the time interval required for the requesting hospital to arrange and transport cryoprecipitate from the central blood service (BSG) and also ensured packs 1 & 2 were not intentionally held back whilst waiting for arrival of the cryoprecipitate from BSG.

Cryoprecipitate transfusion is subsequently advanced earlier in the protocol once a standby inventory of six units of prepooled cryoprecipitate (equivalent to 30 units of cryoprecipitate) was stocked at participating hospital blood banks from late 2013 onwards. With cryoprecipitate available on-site, hospital clinicians could transfuse cryoprecipitate with MTP pack 2 or earlier, depending on the preparation time needed to thaw the cryoprecipitate; this is reflected in our revised protocol from May 2014 (Fig. 2 – MTP timeline).

Table 2 MTP Transfusion packs – composition/constituents

MTP pack	RBC units	Platelet units	FFP units	Cryoprecipitate[a]	Adjunctive therapy
MTP pack 1	4 units packed RBC	1 unit of Pooled Platelets or 1 unit SDP	4 units FFP	None[a]	Intravenous tranexamic acid 1 g stat dose
MTP pack 2	4 units packed RBC	1 unit of Pooled Platelets or 1 unit SDP	4 units FFP		
MTP pack 3	4 units packed RBC	1 unit of Pooled Platelets or 1 unit SDP	4 units FFP	10 units of Cryoprecipitate[b] or 2 pools of pooled cryoprecipitate[b]	Consider use of recombinant-activated factor VII (dose: 90 μg/kg) with MTP pack 3

[a]Cryoprecipitate is not given with pack 1 and 2 in the initial protocol as this component was not stocked at hospital blood banks (till late 2013) and had to be transported from Blood Services Group (BSG) to the hospitals. Cryoprecipitate transfusion is subsequently advanced to an earlier in the MTP protocol (before MTP pack 3) from May 2014 onwards, intended to be given with Pack 2 or earlier, depending on preparation time required by hospital transfusion laboratory.

[b]Prepared and transported from BSG Blood Transfusion Laboratory.

Investigations during MTP support

Coagulation profile, as well as basic haematological and biochemical parameters, should be monitored throughout the resuscitation [43, 44]; testing should be done at the start of MTP activation and subsequently hourly. Tests include full blood count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and serum fibrinogen concentration. Coagulation testing can be further supplemented with rapid point-of-care visco-elastic haemostatic assays such as TEM® and ROTEM® if available in the hospital. Biochemical tests including arterial blood gas, renal panel (serum urea, creatinine and electrolytes), serum lactate and serum calcium should be performed at least 4–6 hourly. The patient's temperature should be monitored.

Laboratory values are tracked and used to guide additional transfusion requirements; additional haemostatic components and factors can be administered to meet recommended target laboratory values and therapeutic triggers [43, 44] (Table 3).

Implementation of the MTP

Operational elements of the protocol are left intentionally flexible to allow adaptation and customization by

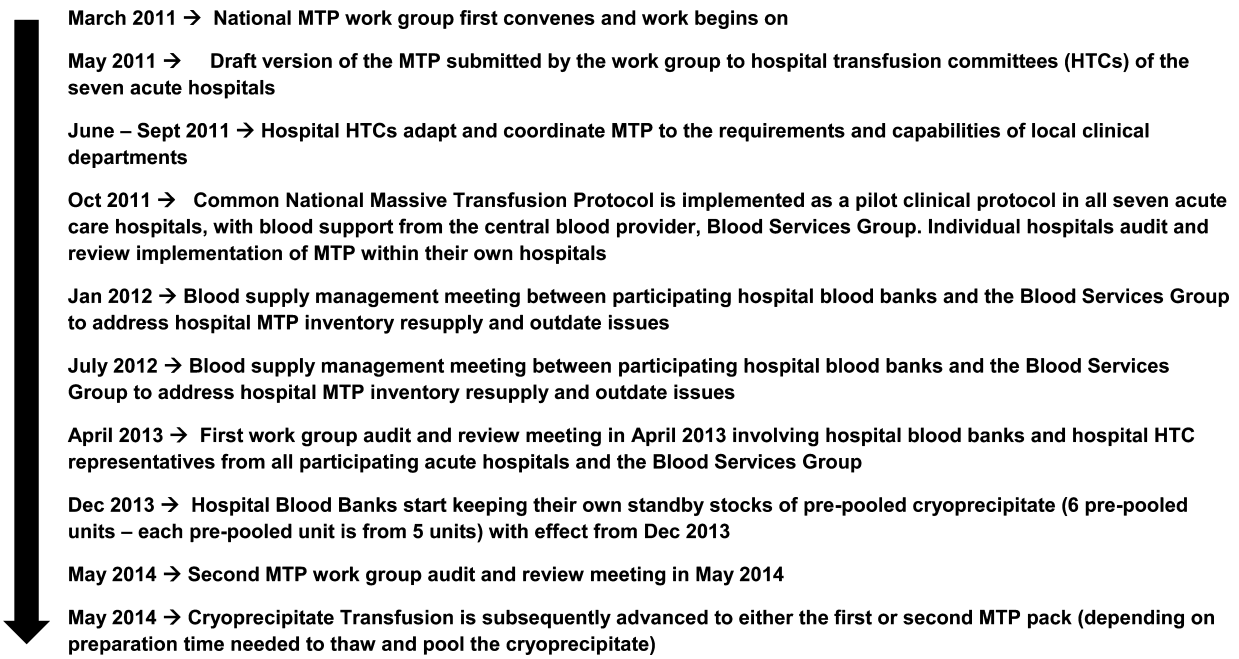

Fig. 2 Timeline of National MTP planning, implementation and review/audit.

Table 3 Recommended target laboratory values (therapeutic triggers)

Laboratory value	Therapeutic target
Prothrombin time	Keep below 1·5× reference value
Activated partial thromboplastin time	Keep below 1·5× reference value
Platelet count	Keep above 50 × 10^9/l
	Keep above 50 × 10^9/l if CNS trauma or multiple trauma present
Serum fibrinogen concentration	Keep above 1 g/dl
Haemoglobin concentration	Keep above 8 g/dl
Arterial blood gas – blood pH	Keep pH above 7·1
Serum calcium	Keep ionized calcium above 1·13 mmol/l
Body temperature	Avoid hypothermia – Keep body temperature above 35°C[a]

[a]Normothermia should be maintained through use of IV warming devices for infusion fluids, use of a Bair Hugger, and ambient temperature control systems to regulate environmental temperature [43].

individual hospitals to suit institutional workflow and patient type. This includes parameters such as designating MTP activation locations, defining the seniority and clinical discipline of physicians permitted for MTP activation and assuming the role of MTP team leader (Fig. 1).

The final version of the MTP was submitted by the work group in May 2011 to the hospital transfusion committees of the hospitals. An implementation timeline of 9 months was set to allow sufficient time for internal discussion and dissemination of critical information to all stakeholders, including medical, nursing, laboratory and support staff from hospital blood banks and relevant clinical departments. Feedback from hospital stakeholders was gathered by the local hospital transfusion committees and addressed in consultation with the national MTP work group.

Audit and control process

Blood use data related to MTP activation, including MTP inventory component outdate and wastages, is submitted by hospital blood banks to the Blood Services Group every 3–6 months, as part of general blood utilization and inventory management data.

Hospital MTP blood usage data are regularly audited at Blood Services Group. Blood component resupply shortfalls and replenishment delays are quickly remedied; excessive blood component outdate and wastages are also flagged for discussion with the hospital blood bank concerned. Key data audited include: the following (1) the number of MTP-activated cases – total number and numbers in the different subcategories (2) proportion of total hospital blood use due to MTP activation (3) the ratio of blood component transfusion achieved (mean and median) (4) the percentages of activations that cease at MTP packs 1, 2, 3 and beyond (5) the percentage outdate of MTP standby inventory blood components, particularly the platelet units, as well as component wastage due to cancellation of ongoing MTP. This information is collated as annual figures and presented for discussion during annual MTP work group review meetings.

As the MTP is piloted independently and internally by each participating acute hospital as a clinical protocol, the blood provider (BSG) is not privy to clinical outcome and operational quality data (for example – percentage of activations that fail to deliver MTP pack 1 blood components to the patient's bedside within 30 min of MTP activation); these are collated separately from blood utilization figures, for review by the respective individual hospital transfusion committees as clinical quality data.

Results

Review of post-MTP implementation and audit of blood use data

The national MTP was implemented by all restructured hospitals at the end of 2011. It was enthusiastically received by clinicians of all participating hospitals who appreciated the assured availability of blood components and a structured transfusion protocol in event of a massive bleeding event.

Data from the initial 2 years of implementing the national MTP were collected and analysed by the work group during the first two MTP review meetings held in April 2013 and May 2014 (Fig. 2).

MTP activations and blood utilization

There were 434 MTP activations from Oct 2011 to Oct 2013. 39% of activations were for trauma patients, 30% for major surgical cases with unexpected heavy bleeding 25% were for bleeding GIT and 6% were for peri-partum haemorrhage.

A total of 4211 red cell units, 3170 FFP units, 653 units of pooled platelets, 149 units of single donor platelets (from apheresis platelet donors) and 1847 units of cryoprecipitate were issued to support these activations.

Platelet units provided by Blood Services Group are available as either pooled platelet units (PPLT) from buffy-coat-derived platelet concentrates of four individual whole blood donations, or as single donor platelet (SDP) units from one apheresis platelet donation. PPLT units

and SDP units have a mean platelet count per unit of $3{\cdot}84 \times 10^{11}$ and $4{\cdot}18 \times 10^{11,}$ respectively. One unit of PPLT or SDP is considered adequate for the platelet transfusion of one adult patient in the MTP protocol. Since each pooled platelet units is derived from platelet concentrates from four whole blood donations, one unit of PPLT can be considered equivalent to four whole blood-derived platelets (WBDP). One SDP unit has a higher platelet count than a pooled platelet unit; it is approximately the equivalent of 0·92 pooled platelet units or 4·35 whole bleed-derived platelet (WBDP) units in terms of platelet count, based on the mean and median platelet counts of these platelet units. Therefore, the platelet components issued for MTP activations from October 2011 to October 2013 (653 units of pooled platelets, 149 units of single donor platelets from apheresis platelet donors) are estimated to be equivalent to 3260 WBDP units.

The mean transfusion ratio achieved was as follows:

1 red cell unit: 0·8 units of FFP

1 red cell unit: 0·8 units of whole blood-derived platelets (WBDP)

1 red cell: 0·4 units of cryoprecipitate

MTP activations accounted for approximately 1·95% of total red cell usage, 4·9% of total FFP usage, 2·6% of total platelet usage and 1·79% of all cryoprecipitate usage during the period reviewed. For the individual hospitals, MTP red cell usage ranged from 1% to 6·5% of total hospital red cell use.

Profile of participating hospitals and patient types requiring MTP activations

Although six of the participating acute restructured hospitals treated trauma patients, only three hospitals are designated level one trauma centres. Amongst the three level one trauma centres, two are tertiary hospitals, whilst one is a secondary hospital. One of the hospitals (hospital G) is an obstetric and gynaecology hospital that did not report any MTP activations for trauma cases.

The MTP case profile (trauma vs. normal trauma MTP activation cases), blood usage and transfusion ratios achieved (red cell to FFP and platelet ratio) differed between participating hospitals (Table 4). The MTP activations at hospital G were only for peripartum haemorrhage (74·1%) and unexpected heavy bleeding during gynaecological surgery (25·9%); their MTP achieved a transfusion ratio of 1 RBC unit: 0·5 FFP unit: 0·9 platelet unit: 0·4 cryoprecipitate unit.

MTP pack utilization

Unsurprisingly, the percentages of cases that deactivated at MTP pack 1 and at pack 2, or proceeded to pack 3 and beyond, differed between the hospitals (Table 5). Most notably, the percentage of MTP-activated cases that do not progress beyond MTP pack 1 of blood components was significantly lower at 27% in the level one trauma hospitals compared to 66% at the non-level one trauma hospitals ($P < 0{\cdot}0001$ by both Fisher's exact test and chi-squared test).

Operational challenges in implementing the national MTP

Blood components sufficient to meet packs 1 and 2 of MTP activation are maintained in each hospital, with replenishment from the central service within 2 h of utilization of standby inventory. To avoid wastage of platelets maintained as standby MTP inventory, a number of practical measures were introduced shortly after the implementation of the national MTP. This included the following:

(1) Issuing platelet units that have at least 3 days of shelf life for hospital MTP inventory standby stock.
(2) Redistributing standby stocks of platelets and red cells 2 days prior to expiry date to other patients and replenishing with new stocks with longer shelf life.

Although there were a few minor supply issues in the initial 1–2 months, these were quickly resolved. Expired blood component wastage was at an acceptable level (annual overall outdate remained below 3% for platelets and below 0·5% for red cells in the 2 years following MTP implementation, 2012 and 2013).

Improvement in blood availability and a shortened blood delivery time observed after implementation of MTP protocol

During routine six-monthly blood supply management meetings, hospital blood banks of the participating hospitals verified that the national blood service was able to fully stock standby MTP inventory in all hospitals at least 90% of the time. They also confirmed replenishment of depleted MTP standby inventory was completed within the stipulated 2 h close to 95% of the time.

During the annual MTP review meetings in April 2013 and May 2014, representatives of all participating acute hospital transfusion committees gave feedback of high clinician satisfaction with the level of transfusion support following MTP activation for urgent critical bleeding cases. In addition, hospitals also reported improvement in the speed of delivery of blood components to massive haemorrhage patients. Obstetric hospital G reported an impressive 50% decrease in mean time from blood request to transfusion of first blood component, from a mean of 45 min (pre-MTP introduction) in the 6 months prior to

Table 4 MTP Activation Profile of Participating Hospitals from October 2011 to October 2013

Level 1 trauma hospitals	Hospital A (%)	Hospital B (%)	Hospital C (%)
Total MTP cases	81	104	34
Trauma	18 (22·2)	33 (31·7)	21 (61·8)
Surgical	28 (34·6)	44 (42·3)	11 (32·3)
Medical	32 (39·5)	25 (24)	2 (5·9)
Obstetric bleeding (includes both antepartum and postpartum haemorrhage)	3 (3·7)	2 (1·9)	0
Mean blood usage per MTP case			
RBC units	9	13	13
FFP units	7	10	10
Whole blood-derived platelets (WBDP)	8	10	11
Cryoprecipitate units	3	7	7
Median blood usage per MTP case			
RBC units	7	10	12
FFP units	4	8	8
Whole Blood-derived platelets (WBDP)	4	8	8
Cryoprecipitate units	10	13	10
Mean transfusion ratio achieved			
Red cell units:FFP units:WBDP units:cryoprecipitate units ratio	1: 0·7: 0·9: 0·4	1: 0·7: 0·8: 0·5	1: 0·7: 0·8: 0·6
Median transfusion ratio achieved			
Red cell units:FFP units:WBDP units:cryoprecipitate units ratio	1: 0·6: 0·6: 1·4	1:0·8: 0·8: 1·25	1: 0·7: 0·7: 0·8

Non-Level 1 trauma hospitals (Hospital G is an obstetric hospital)	Hospital D (%)	Hospital E (%)	Hospital F (%)	Hospital G (%)
Total MTP cases	107	74	7	27
Trauma	62 (57·9)	34 (45·9)	2 (28·5)	0 (0)
Surgical	19 (17·8)	18 (24·3)	3 (43·0)	7 (25·9)
Medical	25 (23·4)	22 (29·7)	2 (28·5)	0 (0)
Obstetric bleeding (includes both antepartum and postpartum haemorrhage)	1 (0·9)	0	0	20 (74·1)
Mean blood usage per MTP case				
RBC units	7	8	7	7
FFP Units	6	6	6	4
Whole blood-derived platelets (WBDP)	6	7	3	6
Cryoprecipitate units	2	4	2	3
Median blood usage per MTP case				
RBC units	5	6	6	6
FFP units	4	5	4	4
Whole blood-derived platelets (WBDP)	4	4	4	4
Cryoprecipitate units	10	10	0	10
Mean transfusion ratio achieved expressed as				
Red cell units:FFP Units:WBDP Units:cryoprecipitate Units Ratio	1: 0·8: 0·8: 0·2	1: 0·8: 0·8: 0·2	1: 0·9: 0·6: 0·3	1: 0·5: 0·9: 0·4
Median Transfusion Ratio Achieved expressed as				
Red cell units:FFP units:WBDP units:cryoprecipitate units ratio	1: 0·8: 0·8: 2	1: 0·8: 0·7: 1·7	1: 0·7: 0·7: 0·0	1: 0·7: 0·7: 1·7

MTP introduction, to a mean of 24 min in the 6 months post-MTP introduction. Another hospital (hospital B, a Level 1 trauma centre) achieved a significant reduction in mean time from blood request to issue of the first blood component from the hospital transfusion service, improving a mean time of 28 min in the 6 months before MTP was introduced, to a mean time of only 18 min after MTP introduction, in the 12 months post-MTP implementation. The non-level 1 trauma hospitals also had similar improvements in turnaround time for blood requests, with hospital D reporting a remarkable mean time of 15 min from blood request to transfusion of first blood component during their first post-MTP introduction year (2012).

Assessment of impact of MTP on national blood supply

An early concern with the implementation of the national MTP was the possibility of an increase in blood component usage. Contrary to expectations, there was no signif-

icant rise in overall red cells and FFP usage following implementation of the National MTP. For the purpose of comparing the blood utilization rate before and after MTP implementation, we evaluated the blood component utilization rate per 100 000 (population) in 2010 before the national MTP implementation and in 2012, after MTP implementation (Table 6): In 2010, the red cell and FFP usage was 1830 units and 658 units per 100 000 (population), respectively. In comparison, the red cell and FFP usage in 2012 was very similar at 1906 units and 621·8 units per 100,000, respectively ($P > 0·05$ by chi-squared test with Yates correction). There was also no significant difference in the usage of either group AB FFP or overall platelet usage between 2010 and 2012 ($P > 0·05$ by chi-squared test with Yates correction).

There was, however, a significant increase in usage of Group O red cells per 100 000 population ($P < 0·05$ by chi-square test with Yates correction) (Table 7). The usage of cryoprecipitate also more than doubled, from 22·8 units of cryoprecipitate per 100 000 in 2010 to 53·9 units per 100 000 in 2012. This increase can be partly attributed to the increased awareness of acquired hypofibrinogenemia in massive bleeding with the widespread adoption of a common MTP and the inclusion of cryoprecipitate in the protocol MTP packs as fibrinogen replacement.

Table 5 Percentages of MTP cases that were deactivated in MTP packs 1, 2 or progressed to pack 3 and beyond

Hospital	Stopped at Pack 1, %	Stopped at Pack 2, %	Stopped at Pack 3 & Beyond, %
A	33	25	42
B	31	23	46
C	0	19	81
All Level 1 trauma centres (Hospitals A, B and C combined)	27	23	50

Hospital	Stopped at pack 1, %	Stopped at pack 2, %	Continued to pack 3 & beyond, %
D	70	19	11
E	63	25	12
F	50	25	25
All non-level one trauma centre hospitals (Hospitals D, E and F combined)	66	11	23
G (an obstetrics & gynaecology hospital)	37	26	37

Discussion

The introduction of a national MTP was a successful collaborative effort of the national blood service with all the major public hospitals in Singapore. It is the first time, a

Table 6 Comparing usage of blood components in 2010 (the year before MTP implemented) with usage of blood components in 2012 (the year after MTP was implemented)

Year	Red cells	FFP	Platelets	Cryoprecipitate
Year 2010				
Gross usage (Per 100 000 Usage)	92 895 units (1829·2 units)	33 403 units (685·0 units)	Total usage was 9756 single donor platelets (apheresis) and 10 255 pooled platelets, which is the equivalent to 83 459 units of whole blood-derived platelets (WBDP units)[a] (1644 WBDP units)	1159 units (22·8 units)
Singapore's resident population in 2010 was 5,076,700				
Year 2012				
Gross usage (Per 100 000 Usage)	101 233 units (1905·6 units)	33 032 units (621·8 units)	Total usage was 10 511 single donor platelets (Apheresis) and 10 906 pooled platelets, which is the equivalent to 89 347 units of whole blood-derived platelets (WBDP units)[a] (1682 WBDP units)	2865 units (53·9 units)
Singapore's resident population in 2012 was 5,312,400				

[a]One SDP unit is approximately the equivalent of 0·92 pooled platelet units or 4·35 whole blood-derived platelet (WBDP) units in terms of platelet count, based on the mean and median platelet counts of both types of platelets. One pooled platelet unit can be considered the equivalent of 4 WMDP units (pooled from platelet concentrates of four whole blood donations).

Table 7 Comparing usage of group of Group O red cells and Group AB FFP in 2010 (the year before MTP implemented) with usage of blood components in 2012 (the year after MTP was implemented)

	Group O Red cell usage	Group AB FFP usage
2010	40 510 units	2600 units
Gross usage (Per 100 000 usage)	(8·0 units)	(0·5 units)
2012	45 195 units	2585 units
Gross usage (Per 100 000 usage)	(8·5 units)	(0·5 units)

common transfusion protocol has been universally adopted by all major hospitals in Singapore. The successful implementation augurs well for further collaborations and introduction of more common clinical transfusion protocols on a national level.

For the national blood service, having a national standardized MTP is advantageous for planning and provision of an efficient blood supply system to support massively bleeding patients. The use of common terminology and pathway also helped to ensure effective communication between clinicians, hospital blood banks and the national blood service.

For our hospitals, they were assured of an adequate supply of standby blood for bleeding emergencies. Another advantage of a common transfusion protocol is to raise transfusion standards and care of massively bleeding patients across hospitals. In addition, this national MTP also facilitated regular hospital internal clinical audit, sharing of blood use data for national review and comparison of practices across the various hospitals. We have observed constructive exchange of ideas and suggestions to improve the national MTP through our work group.

However, implementing a national MTP necessitates reconciling differing transfusion practice across several healthcare institutions. This is made easier by us being a small city state with a close knit medical community working in a limited number of institutions. One of the biggest challenges encountered when drawing up our MTP was to have a protocol easily adaptable to individual hospitals, without deviating from core elements; success was dependent on gaining consensus alignment of all stakeholders to key common features and close co-ordination between the blood service provider, hospital blood banks and clinical teams.

A common protocol does not translate to uniform clinical implementation across all hospitals. This is reflected in differences in the average blood use per patient and the proportion of activated MTP that terminated in pack 1, pack 2 or proceeded to pack 3 and beyond. Possible reasons are differences in the types of bleeding patients handled, clinicians' experience in managing massive haemorrhage and trauma patients, activation criteria adopted by the institution, and the experience of the clinician permitted to activate the MTP. The significant difference ($P < 0{\cdot}0001$ by both Fisher's exact test and chi-squared test) observed in the percentage of activations stopping at pack 2 in the level 1 trauma hospitals (50%) and the non-level 1 trauma hospitals (77%) may be due to some extent to the greater experience in treating trauma bleeders at level one trauma hospitals.

The high proportion of MTP activations that did not progress beyond pack 2 (8 units of red cells, 8 units of FFP and 2 units of pooled platelets or SDPs) in most hospitals are a cause for concern as the majority of these cases represent unnecessary MTP activations or 'overactivations', since they did not fulfil the classical definition of 'massive transfusion' of 10 units of red cells transfused within a 24-h period. This highlights the need to improve MTP triaging and activation.

One possible reason for our high rate of MTP overactivation is the broader coverage of the local MTP protocol to both trauma and non-trauma bleeding patients. In the literature, hospitals implementing hospitalwide MTPs covering both trauma and non-trauma bleeders observed a larger proportion of MTP overactivation [38–40, 50]. Morse *et al*. [50] found overactivation was higher in non-trauma than trauma patients (51% vs. 29%, respectively) over a 4-year period under a hospitalwide MTP that permitted activations for a range of non-trauma bleeding conditions. Overactivation rate is expectedly higher under MTPs that cover both trauma and non-trauma patients since the widely heterogeneous exsanguinating aetiologies seen in non-trauma patients are a major obstacle to accurately predicting likelihood of massive transfusion [48, 50], with a lack of validated predictive scores to objectively triage non-trauma bleeding patients to high likelihood of massive transfusion. Standardizing a common set of clinical criteria for activation of the MTP in non-trauma patients may be one possible solution. Use of massive transfusion algorithms incorporating point-of-care visco-elastic haemostatic assays (TEM® or ROTEM®) could also aid decision-making in MTP activation [46]; these tests show promise as predictors of massive transfusion in recent papers [45].

Even institutions with trauma-only MTP protocols report a fair proportion of MTP overactivation. Dente and colleagues describe overactivation rate of 27% in civilian trauma cases involving torso gunshot wounds [58]. The accuracy of predicting likelihood of massive transfusion in bleeding trauma patients was found to be surprisingly low, at below 60%, despite use of validated scoring systems such as the Assessment of Blood Consumption Score (ABC) and the Trauma Associated Severe Haemorrhage

Score (TASH), according to a study by Subramaniam *et al.* [59].

Accurate triage and correct activation of MTP protocols is important since administration of large volumes of plasma is associated with a substantial increase in transfusion-related complications. Transfusion of increased plasma and platelets ratios confers no survival benefit and may be harmful to patients who do not require massive transfusion, with some studies suggesting that such transfusion reduces mortality in trauma patients at high risk of death but increases mortality instead in those at low risk [60, 61]. Perel *et al.* [61] analysed data from the CRASH 2 study and found transfusion was associated with an increase in death from all causes amongst patients who had a 20% or lower predicted risk of death, but it was associated with a decrease in mortality risk for those patients with a higher than 50% predicted risk of death; transfusion was also linked with more than double the risk of fatal and non-fatal vascular events. Sambasivan and colleagues reported fewer ICU-free days and ventilator-free days in non-massively transfused trauma patients transfused with increased plasma or platelets to red cells beyond a ratio of 1:2 to red cell [62]. Sariani *et al.* [63] reported that transfusion of plasma was associated with an increased risk of infectious complications amongst non-trauma surgical intensive care patients.

We plan to study the clinical practice and operational implementation of the MTP within the various hospitals in the coming 2 years to establish the key reasons for the different rates of MTP overactivation observed between hospitals; our aim is to identify the root causes for incorrectly triaged MTP activation and share best practices that can help decrease the overall rate of MTP overactivation, as well as lower the variation in MTP overtriage rates across different hospitals. This would require joint review of both blood usage audit data, as well as information on patient clinical outcome and operational quality data. The latter two are currently not made available outside of the individual hospital collating the information. The workgroup will therefore actively engage participating hospitals to contribute more information on these specific areas since sharing of clinical and operational input by all hospitals with the blood provider and MTP work group translates to more effective audit and analysis on a national level. We hope to reduce the number of inappropriate MTP activations with better auditing, regular review, effective feedback and training.

Conclusion

From our experience, implementation of a common MTP across several hospitals is feasible, given a shared blood supply system from a centralized blood service supporting all hospitals, as well as proximity of the participating hospitals to the blood service. Factors critical to the setting up of a common transfusion pathway include the following:

(1) Good communication between all stakeholders.
(2) Participation of all stakeholders from the earliest stages of planning to foster a sense of joint ownership and common purpose.
(3) A common protocol that is simple to implement and recall, yet flexible enough to cater to the needs of individual hospitals and specific patient groups.
(4) Sufficient time and resources for dissemination of critical information from the working group and Hospital Transfusion Committees to all end-users.

A nationally shared transfusion protocol cannot be applied in many parts of the world for practical reasons. Centralized blood supply is not possible in some areas due to size, distance and geography, whilst regional differences in blood supply, clinical practice, and transfusion policies makes it difficult to co-ordinate and administer a common protocol within a large country or state. However, a similar programme to implement a national MTP is possible in small states with a compact healthcare system of hospitals in close proximity and supported by a centralized blood service, likely with the same logistical and operational advantages. Examples would be cities, small states and island polities such as Hong Kong, Malta, Macau, Monaco, Qatar and Bahrain. The key to successful application would be flexible adaptation to suit local situation and need, without losing the key elements of the original.

Transfusion resuscitation following massive haemorrhage is a rapidly advancing area of practice. The clinical benefit of applying massive transfusion protocols to non-trauma patients remains to be proven by clinical studies [37, 48, 50]. There is insufficient understanding and evidence to guide the design of separate MTP protocols with optimal blood component transfusion ratios targeted to correct the specific and differing coagulation disturbances found in trauma and non-trauma critical bleeding of the different aetiologies. Institutions who wish to implement inclusive 'hospitalwide' MTP protocols covering trauma, medical, surgical and obstetric patients with massive bleeding are therefore limited to using trauma-based MTP protocols without much alternative option [37, 48, 57].

Extending MTP to non-trauma medical and surgical bleeding patients can increase over-activation of MTP, blood requirement and risk of transfusion complications from large transfusions of plasma [38–40, 50, 60–63]. Recognizing this, our national MTP workgroup will work closely with our hospital partners and together learn from the clinical, blood use and operational data gathered from use of this protocol to improve decision-making in MTP activation, decrease over-activation rates and improve patient care under the common MTP protocol.

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