Guidelines for the Use of Fresh Frozen Plasma Based on Scientific Evidence

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Circumstances of preparation

In 2013, this project was initiated by the Task Force for the Preparation of the Guidelines for the Use of Fresh Frozen Plasma, which is a subcommittee of the Task Force Committee on the Guidelines for the Use of Platelet Transfusion Preparations of the Japan Society of Transfusion Medicine and Cell Therapy, superceded in March 2014 by the Study Concerning the Preparation of Transfusion Guidelines Based on Scientific Evidence, a project subsidized by a Health and Labour Sciences Research Grant and the Japan Agency for Medical Research and Development (AMED). Members of the task force for the preparation of guidelines concerning FFP were selected in consideration of their expertise in May 2013 by the Board of Executives of the Japan Society of Transfusion Medicine and Cell Therapy. In this operation, clinical questions (CQs) were

set, not only for the quality of evidence (each paper), but also the “outcome: usefulness regarding the relevant CQ” was evaluated, and the strength of recommendation was determined over 3 years, with the aim that the guidelines obtained lead to final large-scale revision of the “Guidelines” based on accurate evaluation of the evidence. The Study Concerning the Preparation of Transfusion Guidelines Based on Scientific Evidence issued the final report in March 2016, and the Ministry of Health, Labour and Welfare made a major revision of the “Guidelines for the Use of Blood Products” in March 2017 based on the results of the series of operations.

Although the Guideline for the Use of Fresh Frozen Plasma (FFP) Based on Scientific Evidence was published in 2017, the Guideline Committee began to revise a series of guidelines starting April 2016 while simultaneously initiating the AMED R&D project, “Study of the Use of Blood Products and Implementation of Transfusion Therapy to Further Promote their Proper Use.” The development of modern clinical care is remarkable, and for the proper use of blood products based on the latest knowledge in Japan, it is necessary to pursue a cycle of continuous collection of evidence → assessment → integration → recommendation, and update the guidelines. The present guidelines include new evidence that has become available since 2015 to supplement previous evidence and aims to propose more proper usage of FFP by reconstituting and reevaluating the evidence as a whole.

Committee members

Guideline Committee of the Japan Society of Transfusion Medicine and Cell Therapy

Chairperson: Masanori Matsumoto, Nara Medical University

Project funded by Health and Labour Sciences Research Grants

AMED R&D Operations

“Study of the Use of Blood Products and Implementation of Transfusion Therapy to Further Promote their Proper Use”

Representative: Chairperson: Tadashi Matsushita, Nagoya University

Task Force Committee on the Guidelines for the Use of Fresh Frozen Plasma

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Member: Yoshiko Tamai (Hirosaki University Hospital)

Member: Yuichi Hasegawa (University of Tsukuba)

Member: Masanori Matsumoto (Nara Medical University)

Member: Shigeki Miyata (National Cerebral and Cardiovascular Center)

Member: Satoshi Yasumura (University of Toyama)

Member: Koji Yamamoto (Saitama Medical University)

COI to be disclosed and the roles of members of the guideline preparation committee

Tadashi Matsushita: lecture honoraria (Bayer Yakuhin Ltd., Baxalta Japan Limited, CSL Behring, Novo Nordisk Pharma Ltd., Biogen Japan Ltd., Bioverativ Japan), commissioned research fund (Chugai Pharmaceutical Co., Ltd., Novo Nordisk Pharma Ltd.), scholarship donation (Novo Nordisk Pharma Ltd., Baxalta Japan Limited, Pfizer Japan Inc., CSL Behring)

Yoshiko Tamai: none

Yuichi Hasegawa: none

Masanori Matsumoto: donation (Chugai Pharmaceutical Co., Ltd., Asahi Kasei Pharma Corporation, Bayer Yakuhin Ltd.), lecture honoraria (ALEXION, Asahi Kasei Pharma Corporation)

Shigeki Miyata: lecture honoraria (Daiichi Sankyo Company Limited), research funds (Daiichi Sankyo Company Limited, Mitsubishi Tanabe Pharma Corporation)

Satoshi Yasumura: donation (Japan Blood Products Organization)

Koji Yamamoto: none

	Director	Funding	Setting of CQ	Primary literature search	Secondary literature search	Assigned CQ	Preparation of recommendations/comments	Determination of recommendations/expert opinions
Masanori Matsumoto		○	○			3-(2)-2, 3	○	○
Tadashi Matsushita	○	○	○	○	○	1-(1), 2-(2), 3-(1)	○	○
Yoshiko Tamai			○	○	○	2-(1), 3-(2)-5	○	○
Yuichi Hasegawa			○	○	○	3-(2)-1, 7	○	○
Shigeki Miyata		○	○	○	○	1-(2)	◯	◯
Satoshi Yasumura			○	○	○	3-(2)-4, 6	○	○
Koji Yamamoto			○	○				

Preparation methods

Clinical Questions (CQs) were set up concerning the guidelines for the use of fresh frozen plasma. The strength of evidence and strength of recommendation for each CQ were determined according to the "Minds Handbook for Clinical Practice Guideline Development 2014."[1)] In preparing the present guidelines, evaluation was made primarily by members assigned to the preparation of each CQ but with participation of all members, and the entire evaluation was supervised by Chairperson Matsushita of the Task Force.

Search of databases

For exhaustive searches, 3 databases, i.e., PubMed, the Cochrane Library, and Ichushi-Web were considered essential. As for MEDLINE, PubMed was used in consideration of the cost.

Establishment of literature searching protocol

For each CQ, a searching protocol was prepared by combining keywords and synonyms (using MeSH, etc.) with cooperation of experts in medical literature searching at the International Medical Information Center (IMIC).

Primary screening

Screening was performed using predetermined literature selection and exclusion criteria. In primary screening, papers that did not match the CQ were excluded according to the title and abstract. Those that were difficult to judge were retained for further consideration. From these papers, a data set for secondary screening was prepared, and the texts of the literature were collected.

Literature management

The literature was electronically retrieved, managed in an integrated fashion, and shared.

Secondary screening

The selection criteria were:

1. Existing clinical practice guidelines
2. Systematic reviews (SRs)
3. Randomized controlled trials (RCTs)
4. Observational studies of a relatively large number of cases

Next, they were classified according to CQs, with PICO (P: patients, problem, population, I: interventions, C: comparisons, controls, comparators, O: outcomes), bias risk, etc., simultaneously evaluated, and listed in a table for the evaluation of evidence as a whole.

Evidence as a whole and its summary

Evidence as a whole was prepared concerning each outcome, and the evidence as a whole integrating the bias risk, non-directness, inconsistency, inaccuracy, evaluation of publication (report) bias, magnitude of the intervention effect, dose-response slope, and possibility of attenuation of the effect by confounding factors (elevation of the evaluation when observational studies are included in the evidence as a whole) was compiled.

For the preparation of the 1st edition, 588 papers were selected by primary screening of 2,759 papers concerning FFP transfusion published in Japan and abroad during the period of 1995-2014. Other important literature and papers necessary for the preparation

of statements were added as hand-searched literature. In the present revised edition, an overall evaluation of 148 papers published since 2015 was made, and the revised 2nd edition of the guidelines was prepared.

Circumstances of Literature Search

Field of search	Literature retrieval			Primary selection			(RBC field only) Selection of papers for new CQs (papers collected by the former Matsushita Group)			Addition by hand search
	PubMed	Cochrane	Ichushi	Papers reviewed	Adopted	Excluded	Papers reviewed	Adopted	Excluded	

Secondary selection • evaluation of each paper			Addition by hand search	Re-adoption after elimination (change to adoption)	Overall evaluation of evidence		
Papers reviewed	Adopted	Excluded			Papers evaluated	Edition	
						Revised	1st

※1 Number of papers after exclusion of duplication among databases from the number of hits returned to the search

※2 In the 4 fields in common with the former Matsushita Group (RBC, WBC, FFP, children), papers adopted by the former Matsushita group were added.

The strength of recommendation is also indicated at 2 levels according to the “Minds Handbook for Clinical Practice Guideline Development 2014”[1]: [1] strongly recommended or [2] weakly recommended. The strength of recommendation is shown with the strength of evidence of the overall outcome (A, B, C, D).

A (strong): There is strong confidence in the estimate of the effect

B (moderate): There is moderate confidence in the estimate of the effect

C (weak): The confidence in the estimate of the effect is limited

D (very weak): There is little confidence in the estimate of the effect

Publication and revision

The present guidelines are published in the journal of the Japan Society of Transfusion Medicine and Cell Therapy and posted on its web site. They will also be revised with the accumulation of scientific evidence.

Funding and conflicts of interest

Funds for the preparation of the present guidelines were obtained from a Health and Labour Sciences Research Grant, and Japan Agency for Medical Research and Development (AMED) Research Program Grant for the “Study Concerning the Preparation of Transfusion Guidelines Based on Scientific Evidence.”

The contents of the present guidelines are not beholden to entities with vested interests associated with pharmaceuticals, biologicals, or medical equipment, whether for profit or not for-profit. Preparation committee members have reported potential conflicts of interest to the Japan Society of Transfusion Medicine and Cell Therapy.

Triggers and recommendations of the use of FFP according to the clinical condition

Major changes in the revision

CQ1-(1)

Evidence in Japan (cardiac surgery, reference 4) was added to the comment.

CQ2-(2)

It was recommended to promptly make the administration ratio of FFP to RBC 1:1, or at least 1:2, and the strength of evidence was raised to 1C. Although some new evidence was added related to proactive FFP administration in MTP, the evidence level was kept as C. However, as the members agreed on a stronger recommendation compared with the previous edition, the recommendation level was changed from 1 to 2.

CQ2-(1)

Reference 25 (evidence in the field of gastrointestinal surgery) was added. Previous comments about efficacy and utilization in FV or FXI deficiency were moved to CQ2-(2)-6.

CQ3-(2)-2

The strength of recommendation of FFP transfusion for congenital TTP was added as 1B.

CQ3-(2)-3

The addition of evidence after 2015 (references 44 and 32) was mentioned in the comment.

CQ3-(2)-4

New evidence concerning acute liver failure (reference 48) was added, and descriptions were added in the comment, but the strength of recommendation was not changed.

CQ3-(2)-6

The former CQ3-(2)-6 (CQ concerning neonates) was deleted in favor of its transfer to the guidelines for pediatric transfusion. Therefore, deficiencies of a single clotting factor (FV and FXI deficiencies) were decided to be advanced as CQ3-(2)-6, and a section concerning the use for congenital FV or FXI deficiency was added.

CQ3-(2)-7

Burns were advanced compared with the previous edition (2-(8)).

CQ5 (How stable is FFP after thawing?) in the previous edition was deleted, because the expiration date for use was extended in 2018.

The number of references was increased from 34 to 50.

CQ1 What constitutes a useful/optimal dose for surgery/trauma that requires massive transfusion?

(1) What PT, APTT, and fibrinogen concentrations are appropriate triggers for FFP transfusion for surgery/trauma that requires massive transfusion?

Recommendation

In surgery/trauma that requires massive transfusion, the prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen concentration are all inadequate as triggers for FFP transfusion to improve the patient outcome. However, as there is no other marker useful as a trigger, FFP transfusion should be considered if these markers continue to decline (2D).

Comment

As a result of evaluation, it was shown that promising evidence concerning this CQ

remains scarce, and even the conclusion that the values conventionally used in Japan should not be maintained was not reached. Thus, no definitive trigger can be set, but provisional triggers will be set according to so-called institutional standards.

Today, clotting factor concentrates are available for the treatment of many congenital clotting factor deficiencies, and the administration of FFP is more narrowly restricted to acquired hemorrhagic tendency. Acquired hemorrhagic tendency often involves multiple clotting factor deficiencies, and the trigger for making decisions of FFP administration must be flexible, according to the clinical condition of each patient. It is practically impossible to determine the therapeutic strategy in consideration of the activity of each clotting factor at each point. The guidelines recommend using a PT ≤30% or INR ≥2.0 and an APTT ≤25% or ≥2 times the upper limit of the reference interval. However, the PT or APTT presented in % is to call the attention of medical staff to prolongation of the clotting time, and does not mean that the activity of all clotting factors is 30% or 25%. Johansson and Stensballe incorporated the results of thromboelastography (TEG) in 832 patients who required red blood cell transfusion of 10 units or more in the algorithm of FFP transfusion, compared the outcomes of these patients with those who received conventional proactive FFP transfusion, and reported a decrease in the early mortality rate.[2)] However, because of marked decreases in the volume of intraoperative hemorrhage and the amount of blood transfusion in patients with hypofibrinogenemia that is corrected, the use of the fibrinogen level as a trigger is gaining favor for patients with massive blood loss.[3)] From Japan, an RCT that evaluated an algorithm using ROTEM in 100 children undergoing cardiac surgery was reported,[4)] and the fibrinogen level measured with FIBTEM was higher in the ROTEM group. EXTEM was also reported to be useful. While these reports do not directly reflect the response-predicting

ability of the PT, APTT, or fibrinogen level, continuation of careful observation is considered necessary, and practical triggers for the decision of intraoperative FFP administration are expected to be necessary in the future.

(2) What is a useful/optimal dose for surgery/trauma that requires massive transfusion?

Recommendation

In initial treatment of patients expected to need massive transfusion, it is recommended to administer FFP and RBC, aiming to achieve a ratio of 1:1 early or at least maintain it at 1:2 (1C).

Comment

Much of the activities of clotting factors are derived from enzyme reactions, which occur in water solutions (liquid phase). Therefore, the concentrations of clotting factors in plasma is more important than those in whole blood for physiologic hemostasis, and clotting factors are not expected to be sufficiently active in a low-hematocrit condition due to blood loss. Moreover, massive RBC transfusion for hemorrhage may make hemostasis difficult due to dilutional coagulopathy, which is an indication for FFP. The “Guidelines for the Use of Blood Products” (partially revised in June 2016) before the revision in 2017 stated, “Intraoperative hemorrhage is managed, in principle, by blood component transfusion as described below depending on the percentage of blood loss relative to the circulating blood volume and clinical findings: Since hemorrhagic tendency due to decreases in clotting factors and the platelet count (dilutional coagulopathy and thrombocytopenia) may be induced by massive transfusion exceeding the circulating blood volume (≥100% within 24 hours) or rapid transfusion (≥100

mL/min), the administration of FFP or platelet concentrates should be considered by referring to the results clotting tests, platelet count, and clinical hemorrhagic tendency." For this reason, FFP and platelet concentrates are considered only in significant blood loss. However, patients with, or at a high risk of, massive hemorrhage, including trauma patients, develop clotting or hemostatic disorder not entirely ascribed to dilutional coagulopathy in a very early stage, and the importance and outcome-improving effect of sufficient early substitution of clotting and hemostatic factors in such conditions have been suggested. Treatment using a massive transfusion protocol (MTP) aiming at prevention, or early correction, of acute consumption/dilutional coagulopathy due to significant blood loss, i.e., early proactive FFP administration, may be effective. However, because massive administration of plasma may induce adverse events including acute lung injury and volume overload, we evaluated whether early proactive FFP administration can be recommended if an MTP is implemented and, if it is recommended, what the optimal plasma/RBC ratio would be like.

MTP makes prompt implementation of transfusion therapy at a previously prescribed ratio possible and makes speedy systematic responses possible. In transfusion at a high plasma/RBC ratio, transfusion is promptly performed at a recommended ratio (e.g., 10 units of thawed FFP, 10 units of RBC, and, if appropriate, platelet concentrates, cryoprecipitate, or fibrinogen preparation arranged as a set) in patients with massive hemorrhage or patients in whom bleeding is likely to be exacerbated to a serious level.

Since patients with massive hemorrhage have a poor prognosis and a high mortality rate, in this CQ, the 28-day (or 30-day) mortality rate, in-hospital mortality rate, or early mortality rate within 24 hours after admission was examined as a major evaluation item, and the necessary volume of transfusion, number of days in the ICU, thromboembolism,

organ damage, and acute lung injury were evaluated as secondary evaluation items concerning the effectiveness of transfusion at a high plasma/RBC ratio.

Trauma patients

First, according to meta-analyses of 2 RCTs in which the effectiveness of MTP was evaluated in patients who have developed, or are at a high risk of developing, massive hemorrhage,[5,6] about whom accumulation of evidence is progressing, and other observational studies,[7-9] the mortality rate tended to be lower in the high plasma/RBC ratio transfusion group except in an RCT in which an MTP used modified whole blood and each preparation at 1:1 was compared as a pilot study[6] and a meta-analyses of before-and-after studies that evaluated the effects of introducing an MTP (including studies in which the implementation of MTP was questionable).[8] In the PROPPR study,[5] which was the only high-quality RCT, the overall mortality rates after 24 hours [12.7% vs. 17.0%, adjusted RR 0.75 (0.52 to 1.08), P= .12] and after 30 days [22.4% vs. 26.1%, adjusted RR 0.86 (0.65 to 1.12), P= .26], which were the primary endpoints, did not differ significantly in the group with a plasma/platelet/RBC ratio of 1:1:1 (high plasma) compared with the 1:1:2 group, but the mortality within 24 hours, which was often due to blood loss, was significantly lower (9.2% vs. 14.6%, P= .03), and the accomplishment of anatomical hemostasis was significantly higher (86% vs. 78%, P= .006), in the 1:1:1 group (high plasma) compared with the 1:1:2 group. The effectiveness of high-plasma transfusion on the 24-hour mortality was also shown by a paper about meta-analysis of observational studies using severity-matched patients.[7] However, in the PROPPR study, thawed plasma (thawed in advance and ready to be used immediately) was always available, and blood products were transported to the patients mostly within 10 minutes after the initiation of MTP upon arrival of the

patients. Thus, MTP using plasma, platelets, and RBC prepared at 1:1:1 is likely to be useful in an environment that permits prompt initiation of transfusion, and sub-analysis of the PROPPR study showed that the time (in minutes) from the patient's arrival to the delivery of blood products first contained in the MTP cooler was an independent risk factor of death within 24 hours and death within 30 days.[10)]

Concerning observational studies, there were only 2 well-arranged prospective studies including the PROMMTT study,[11, 12)] and serious bias risk was noted. Survival bias is particularly crucial. Time is necessary for FFP to thaw, and as the beginning of the administration of FFP is delayed compared with RBC in patients who die early after injury (within 1-2 hours after admission), early death cases inevitably receive transfusion at a low plasma/RBC ratio. In the presence of such a survival bias, a low mortality rate is not necessarily ascribable to the effectiveness a high plasma/RBC ratio.[13)] In observational studies, such a survival bias cannot be completely eliminated, but nearly all studies have indicated that a high plasma/RBC ratio is related to a decrease in mortality, which is notable within 24 hours after admission, during which many deaths are caused by bleeding (particularly within 3-6 hours). Many other studies have also suggested the importance of sufficient administration of plasma in an early period.[14-16)] The effectiveness of achieving a plasma/RBC ratio of >1:1 within 6 hours was also reported by a multicenter collaborative retrospective observational study conducted in Japan.[17)]

In Japan, it is impossible for most facilities to constantly keep a stock of thawed plasma. Therefore, it is considered practical and effective to manage MTP aiming to achieve a plasma/RBC ratio of 1:1 (it is important to create a system for administering plasma as early as possible) and to maintain a ratio of at least 1:2.

Concerning the recommended plasma/RBC ratio, a majority of reports indicate that a plasma/RBC ratio of at least 1:2 is effective, but there are also the results of meta-analysis that no dose-response relationship was observed even when the ratio was increased to 1:1,[7] and inconsistency was found to be present in integration of evidence.

Concerning evaluation items such as the necessary volume of transfusion, duration of the stay in the ICU, thromboembolism, and organ damage, bias risk and inconsistency among studies were serious, and we could not establish consensus.

As for acute lung injury, the number of patients is insufficient for the evaluation of acute respiratory disorders by an RCT. A meta-analysis of observational studies with a high bias risk reported an increase in acute lung injury.[9] However, according to sub-analysis of the PROMMTT study reported thereafter, crystalloid administration increased, but plasma administration did not increase, and early platelet administration reduced respiratory disorders.[18] There is also a report that a high plasma/RBC ratio itself did not increase ARDS[19] (while crystalloids and massive transfusion increase ARDS), and no clear evidence that a high plasma/RBC ratio increases acute lung injury could be obtained.

Surgery

Among studies targeting cardiac surgery, a post-hoc of an RCT that evaluated the effect of storage duration of RBC preparations reported that the overall mortality and multiple organ failure within 28 days after surgery decreased in patients who received a transfusion of 6 units (equivalent to 12 Japanese units) of RBC or a total volume of 8 units within 24 hours after the beginning of surgery when the plasma/RBC ratio was ≥1.[20] Similarly, in the field of cardiac surgery, the results of a retrospective observational study that the administration of FFP and RBC at a ratio of >1 led to a decrease in mortality within 30 days in patients with massive hemorrhage [defined as those intraoperatively transfused

with 8 units (equivalent to 16 Japanese units)] were reported.[21] Concerning patients with ruptured aortic aneurysm, a before-and-after study showed that the mortality within 30 days was significantly reduced by the introduction of an MTP with administration of FFP and RBC at 1:1.[22]

Obstetrics

In the field of obstetrics, the survival rate was reported to be high in patients transfused at an FFP/RBC ratio ≥1 in a nation-wide retrospective case-control study of amniotic fluid embolism by the Japan Association of Obstetricians and Gynecologists (n=54).[23]

Thus, in fields other than trauma, most of the reports are observational studies of a small number of patients with a high bias risk, but the administration of more FFP than RBC units seems to be effective for improving the outcome in patients undergoing surgery of the heart and great vessels or those with amniotic fluid embolism who may develop acute coagulopathy as observed in trauma patients with, or at a high risk of, massive hemorrhage.

Points of attention in clinical application

In circumstances that preclude early administration of plasma or platelets, given that point-of-care TEG or fibrinogen monitoring may be useful, it is necessary at each institution to evaluate how promptly various preparations can be administered after initiating an MTP. It is particularly important to develop an institutional system that makes early administration of plasma possible.

CQ2 What is a useful/optimal dose of FFP transfusion in trauma/surgical patients who do not require massive transfusion?

(1) Is prophylactic FFP transfusion useful in trauma/surgery that does not require

massive transfusion (including chronic liver disease, liver cirrhosis, chronic hepatitis, etc.)?

Recommendation

It is recommended, in principle, not to perform prophylactic FFP transfusion in trauma/surgery that does not require massive transfusion (2B).

Comment

In the work of revision, the search by this committee found no paper with strength sufficient to affect the evidence. There were no papers concerning cost-effectiveness, nor any to suggest that FFP transfusion is beneficial in trauma/surgery that does not require massive transfusion.

According to our latest review, there was no new evidence with strength sufficient to affect recommendations. In this CQ, importance continued to be attached to the number of papers on patients without massive hemorrhage reporting that FFP transfusion is not beneficial or is harmful. Although these were reports of observational studies, among patients with intracranial hemorrhage receiving antiplatelet therapy, deterioration of the long-term outcome in the cohort transfused with FFP is noteworthy.[24, 25)]

If the patient does not have severe coagulopathy, few papers have recommended prophylactic FFP transfusion. Even if the necessary volume of transfusion is selected as the outcome, the effectiveness of FFP transfusion has not been demonstrated, nor can FFP transfusion be considered cost-effective. Moreover, regardless of the necessity of massive transfusion, multiple meta-analyses have shown that FFP transfusion is not superior to fibrinogen preparations[26)] and there is little evidence concerning prophylactic transfusion.[27, 28)]

While there are reports that the mortality rate is increased by FFP transfusion, particularly, in patients without massive hemorrhage, reports that transfusion is beneficial were not found. According to a meta-analysis by Murad et al.,[9] the increase in mortality associated with FFP transfusion in surgical patients not requiring massive transfusion was insignificant (OR, 1.22; 95% CI, 0.73-2.03), but transfusion increased acute lung injury (OR, 2.92; 95% CI, 1.99-4.29). Although these are the results of an observational study, the duration of hospitalization, complications (DIC, venous thrombosis, etc.), and in-hospital deaths were all inferior in the FFP transfusion group compared with the non-transfusion group (P<0.001) in patients undergoing hepatopancreaticobiliary and colorectal surgery.[29]

In consideration of the above, because of the absence of papers that indicate the benefit of FFP transfusion in patients not requiring massive transfusion, FFP transfusion is not recommended from the viewpoint of cost-effectiveness by restricting the targets to those with severe coagulopathy.

(2) Are PT, APTT, and fibrinogen concentration useful before the judgment of the necessity of FFP transfusion in trauma/surgery that does not require massive transfusion?

Recommendation

In mildly invasive procedures (e.g., needle biopsy of the liver, ascites tapping, and CV catheter insertion), the risk of hemorrhage is not increased even in those with prolonged PT, and FFP is not recommended, because its usefulness is considered low. However, in surgery and childbirth involving severe hemorrhage, FFP is administered to those with prolonged PT or APTT or a low fibrinogen level, and their monitoring is recommended at present, although its usefulness is unclear (2C).

Comment

The extent to which clotting tests are abnormal is considered to be greater among patients receiving large doses of FFP, but few studies have shown its relationship with the necessity of FFP administration as evidence similar to CQ1. It is considered difficult to judge the necessity of FFP by clotting tests before hemorrhage. Fenger-Eriksen et al. retrospectively compared a group administered a large dose of FFP and a group administered a smaller dose of FFP and reported no difference in PT or APTT between the two groups and no difference in PT, APTT, or the activities of nearly all the other clotting factors after transfusion[30)]

The strength of recommendation concerning this CQ was determined from the results of retrospective analyses of clinical data including the report that the PT-shortening effect of FFP transfusion was very limited in patients who showed mild prolongation of PT or APTT[31)] and from the guidelines concerning the use of FFP published from 1996 to 2009. However, since the guidelines were based on papers with a small number of patients and mostly retrospective clinical data, the grounds for this recommendation are not strong.

However, in 2016, FFP transfusion at 20 mL/kg was compared with PCC administration at 30 IU/kg in an RCT in patients 18 years and above with cerebral hemorrhage treated within 12 hours after the onset of symptoms and with an INR of ≥2.0.[32)] As a result, a higher percentage of patients achieved an INR of ≤1.2 within 3 hours. Although this result is not consistent with the present CQ, it indirectly indicated that the INR after transfusion can be a prognostic index.

CQ 3 Is FFP transfusion useful for non-surgical patients, e.g., patients with acute pancreatitis, patients with liver dysfunction, severely ill patients in the ICU (not including

those with TTP or DIC)?

(1) Is checking of PT, APTT, and fibrinogen concentration useful before evaluating the necessity of FFP in non-surgical patients (e.g., patients with acute pancreatitis, patients with liver disorder, and severely ill patients in the ICU)?

Recommendation

It is necessary to measure PT, APTT, and fibrinogen and confirm the presence of clotting factor disorders before using FFP. Also, it is significant to compare the values before and after transfusion and judge whether the use of FFP should be continued or not. However, it is difficult to determine the dose of FFP or predict its effectiveness (2C).

Comment

It has been suggested to be necessary in severely ill patients to monitor coagulation parameters such as PT, APTT, and fibrinogen before the use of FFP to confirm the presence of clotting factor disorders.[33] However, similar to the previous CQs, we could not find sufficient evidence concerning the clinical situations assumed in this CQ. We evaluated whether the results of clotting tests before the use of FFP serve as the basis for the judgment of the use of FFP and whether they contribute to the estimation of the dose of FFP. At facilities where tests such as thromboelastography (TEG) and ROTEM are available, it is significant to analyze bleeding diatheses and select appropriate treatments.

Busund et al., conducted an RCT concerning typical FFP transfusion and plasma exchange in a small number of patients admitted to the ICU and reported an improvement in the survival rate by plasma exchange.[34] Despite this RCT, the evidence as a whole is insufficient for constituting a recommendation.

No other promising evidence that affects the recommendation concerning this CQ was

found in the revision of the guideline.

(2) How useful is FFP transfusion in non-surgical patients (e.g., patients with acute pancreatitis, patients with liver dysfunction, severely ill patients in the ICU not including those with TTP or DIC)?

(2)-1 Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Recommendation

For both GBS and CIDP, plasma exchange using FFP as a replacement fluid is suggested to be effective, but plasma exchange using albumin-supplemented lactated Ringer's solution is recommended, and the use of FFP is not, because of the frequent occurrence of adverse reactions such as allergy (1A).

Comment

Functional recovery from neuropathy is the first priority. As a result, the significance of plasma exchange was considered evident. In addition to plasma exchange, intravenous immunoglobulin (IVIg) has been reported to be equally useful for GBP and CIDP, which are neurological disorders. Although plasma exchange using FFP as a replacement fluid is comparably effective, it more often causes complications (adverse effects including hypotension occur in 3-17%), so the use of FFP for GBP and CIDP is not recommended,[35] and this conclusion was maintained in a new systematic review.

(2)-2 Thrombotic thrombocytopenic purpura (TTP)

Recommendation

Plasma exchange using FFP as a replacement fluid is recommended for acquired TTP (1B). While transfusion of FFP alone is effective, plasma exchange is even better. In acquired TTP, plasma exchange using FFP as a replacement fluid should be performed as

early as possible after the diagnosis. FFP transfusion is recommended for congenital TTP since it is presently the only treatment (1B).

Comment

There are 2 types of TTP, acquired and congenital, and acquired TTP is caused by the production of autoantibody to ADAMTS13, an enzyme that cleaves von Willebrand factor (VWF).[36, 37] An RCT that compared plasma exchange using FFP as a replacement fluid and plasma transfusion as treatments for acquired TTP has been reported.[38] Each group consisted of 51 patients, and plasma exchange was clearly more effective according to mortality at 6 months, being 22% in the plasma exchange group and 37% in the plasma transfusion group. In acquired TTP, mortality without treatment is ≥90%.[39] The effectiveness of plasma exchange for acquired TTP may be ascribed to elimination of ADAMTS13 autoantibody and ultrahigh molecular weight VWF polymer, replacement of ADAMTS13, etc.[40] In an RCT that compared the effects of cryosupernatant, which is reported to contain a large amount of ADAMTS13,[41] and FFP, no difference in the survival rate was observed.[38] Also, plasma exchange using albumin as a replacement fluid is not recommended, because ADAMTS13 cannot be replaced. Since replacement of ADAMTS13 alone is effective for congenital TTP, supplementation of FFP, which is presently the only product available, is medically reasonable, although its evidence has not been established.[42] No evidence concerning treatment for TTP using FFP was found in the work of revision.

(2)-3 Warfarin reversal

Recommendation

Concerning warfarin reversal, the effect of FFP on the coagulation system is clearly partial, and there are no grounds for its use in the absence of severe hemorrhage. FFP

administration is not recommended for emergency warfarin reversal. Vitamin K is usually administered, but, if emergency reversal is necessary, the use of a prothrombin complex concentrate rather than FFP is recommended (2C).

Comment

FFP administration is not recommended for emergency warfarin reversal.[43] Vitamin K is usually administered, but if emergency reversal is necessary, the use of a prothrombin complex concentrate rather than FFP is recommended. Evidence has accumulated since 2015, and according to a SR of 13 studies before 2015 that compared PCC and FFP (5 RCTs and 8 observational studies),[44] PCC was superior in overall mortality (odds ratio: 0.56, 95% CI: 0.37–0.84, p=0.006) and normalization of the INR (odds ratio: 10.80, 95% CI: 6.12–19.07). In addition, the risk of volume overload is lower in patients administered PCC compared with FFP (odds ratio: 0.27, 95% CI: 0.13–0.58), and no difference was observed in the incidence of thromboembolism after administration. In 2016, the results of an RCT targeting intracranial hemorrhage associated with warfarin overdose alone were disclosed.[32] Allocation was made by the envelope method. The endpoint was the percentage of patients in whom the INR decreased below 1.2 within 3 hours, and the results were masked. The endpoint was reached in only 9% of the patients in the FFP group, but as it reached in 67% of the patients in the PCC group, the trial was cancelled before a significant difference was observed in the survival rate.

As yet, FFP has not been used generally for this purpose, and it has been used only when PCC is not available, but a PCC preparation covered by health insurance has also entered the market in Japan.

(2)-4 Liver injury

Recommendation

There is little scientific evidence that FFP is effective for liver injury. FFP is empirically used for the treatment of severe liver injury, and it may be effective if prolongation of PT or hemorrhagic symptoms are present or for acute liver failure (2C).

Comment

It is necessary to discuss clotting abnormalities in severe liver injury in consideration of not only the decrease in production of clotting factors in the liver but also decreases in platelets and the production of anticoagulant factors, fibrinolytic factors, and antifibrinolytic factors by the liver. This stance is partially supported by by Tripodi et al., that the results of the thrombin generation test (TGT) were normal in liver cirrhosis patients.[45)] On the other hand, Mueller et al. maintain that, to perform invasive treatments in patients with liver disorders, PT should be ≥50% or <1.5 times the normal value.[46)] However, in an RCT in which rFVIIa (NovoSeven®) was administered to 245 liver cirrhosis patients, PT was markedly shortened as expected, but the superiority of its clinical hemostatic effect could not be demonstrated.[47)] In addition, it is obvious that the presence of portal hypertension in liver cirrhosis is related to visceral hemorrhage, which is often observed in such patients. In general, data of coagulation studies are not considered satisfactory to set a trigger for FFP administration for severe liver disorders.

Acute liver failure (ALF) has a poor prognosis, and only liver transplantation is considered lifesaving. Plasma exchange has been conducted as an internal treatment, but it is a palliative therapy against symptoms of liver failure such as bleeding and coma. It has been seen to cause emergence from coma or improvement in PT but not to contribute to prolongation of the life-span. Larsen et al. prospectively evaluated the effect of high-

volume plasma exchange (HVP) in 182 patients with acute liver failure using those receiving standard conservative treatment as a control group.[48] The overall survival rate was 58.7% in the HVP group and 47.8% in the control group (HR of liver transplantation: 0.56, 95% CI: 0.36–0.86, p = 0.0083), and the prognosis was expected to be poor, but the survival rate was significantly higher in the HVP group even in those who did not receive liver transplantation. Also, the INR and biochemical data, such as bilirubin, ALT, and ammonia, SIRS score, and SOFA score, were significantly lower in the HVP group compared with the control group. Since HVP is suggested to increase the survival rate in ALF patients not given liver transplantation, further studies are awaited.

(2)-5 Acute pancreatitis

Recommendation

FFP administration is not recommended for acute pancreatitis (2C).

Comment

No report of the use of FFP for acute pancreatitis was found also during the additional literature search period for the revision of the guidelines, and 2 reports published before the search period[49, 50] were used as references. As a result, since no improvement in the laboratory test results or prognosis was observed compared with albumin administration, the administration of FFP for acute pancreatitis is not recommended.

(2)-6 Single clotting factor deficiencies (factor V, factor XI deficiencies)

Recommendation

While evidence is scarce, prophylactic transfusion is considered to be medially reasonable despite the lack of evidence. (No recommendation grade)

Comment

The present guideline states, “Although concentrates of respective clotting factors are

used, in principle, for the treatment of clotting factor deficiencies, concentrates for factor V or factor XI deficiency are currently unavailable. Therefore, FFP is indicated for deficiency of either of these factors alone or deficiencies of multiple factors including them for hemorrhagic symptoms or invasive treatments." Therefore, prophylactic transfusion is considered acceptable as medically reasonable despite the lack of evidence.

(2)-7 Burns

Recommendation

The use of FFP for objectives including the prevention of infection in severe burns is not recommended.

Comment

Since no report that evaluated the usefulness of FFP in burns was found during the literature search period, the use of FFP for burns is not recommended, consistent with previous editions.

*In this revision, DIC, a non-surgical disorder, was not adopted as a CQ as in the previous editions. Needless to say, the first priority in the therapeutic strategy for DIC is treatment of underlying disorders, but, partially because of the complexity of underlying disorders, there is little RCT-based evidence concerning FFP replacement therapy exclusively for DIC. In DIC patients, clotting factors, anticoagulant factors, and fibrinolytic factors are consumed at a very high turnover rate, and, in such a disease state, transfusion of FFP containing "all" is considered acceptable along with platelet transfusion and cryoprecipitate as medically reasonable options.

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