BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 29 1940

VOLUME AND RATE IN BLOOD TRANSFUSION FOR THE RELIEF OF ANAEMIA

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Although blood transfusion has been in use for many years curiously little attention has been paid to the questions of how much blood should be given and at what rate. It has become customary to "give a transfusion," meaning about a pint (568 c.cm.) in about half an hour. This practice is irrational and unsatisfactory. In every transfusion the volume of blood to be administered and the rate of administration should be matters of primary importance. The purpose of the present study is an attempt to supply principles. Transfusion for the relief of anaemia uncomplicated by acute haemorrhage is chosen for discussion because it brings out points important also in relation to transfusion for other purposes. The main general principles which will be submitted regarding transfusion for anaemia are that benefit is dependent upon adequacy of volume and safety upon slowness of administration.

Material

For several years we have made a special study of the problems of volume and rate in transfusion. It was to render technically possible the administration of any volume of blood at any rate, but particularly of large volumes at very slow rates, that we devised our method of continuous-drip blood transfusion (Marriott and Kekwick, 1935, 1937). The present paper is based on the analysis of 194 drip transfusions for anaemia (see Table I), of which 177 were to adults and seventeen to children. Ninety-nine were done by ourselves, while ninety-five were performed by colleagues, at the Middlesex Hospital from 1935 to 1938, when each of us in turn was resident medical officer there and followed up the cases.

Purpose and Indications of Transfusion for Anaemia

Anaemia is haemoglobin deficiency. The essential purpose of transfusion for the relief of anaemia is the provision of haemoglobin. Such aims as the supply of anti-haemorrhagic, haemopoietic, or immunological factors are outside the scope of this paper. Transfusion should not be used to restore haemoglobin deficiency that can be treated successfully by ordinary measures (iron, liver, etc.). Special circumstances are needed to make it justifiable—namely:

1. When there is no time to wait upon the slow action of haemopoietic remedies.—(a) When anaemia is

TABLE I.—Distribution with regard to Indications and Conditions of 194 Drip Transfusions for Anaemia Uncomplicated by Acute Haemorrhage

1a. Dangerously severe anaemia	32
Leukaemia	10
Hypoplastic or aplastic anaemia	7
Chronic bleeding	4
Idiopathic hypochromic anaemia	4
Subphrenic abscess	2
Acholic jaundice	1
Puerperal sepsis	1
Pelvic abscess	1
Ulcerative colitis	1
Pernicious anaemia	1
1b. Anaemia complicated by some emergency :	
(i) Unavoidable major operations	45
Gastric ulcer	3
Hour-glass stomach	1
Anastomotic ulcer	1
Carcinoma of stomach	14
Stenosis of common bile duct	2
Splenectomy for purpura	2
" " splenic anaemia	1
" " acholic jaundice	1
Colitis with stricture	1
" " gastro-colic fistula	1
Laparotomy	1
Carcinoma of caecum	3
" " colon	3
" " rectum	1
Pyonephrosis	1
Carcinoma of bladder	1
Enlarged prostate	1
Chronic menorrhagia and fibroids	3
Carcinoma of cervix uteri	1
Malignant ovarian cyst	1
Amputation of infected leg	1
Sarcoma of buttock	1
(ii) Unavoidable minor operations in patients with anaemia and bleeding tendency	3
Dental abscess	2
Epistaxis	1
(iii) Radium or x-ray treatment (urgent)	10
Carcinoma of cervix uteri	7
" " oesophagus	1
" " stomach	1
" " mandible	1
(iv) Pregnancy almost at term	2
1c. Anaemia in patients whose recovery is urgent for special reasons :	
Chronic bleeding	1
2a. Aplastic and allied anaemic states	57
Hypoplastic or aplastic anaemia	33
Myeloclerosis	5
Multiple myelomatosis	1
Leukaemia	12
Hodgkin's disease	4
Splenic anaemia	2
2b. Anaemia in septic and infective conditions	44
Ulcerative colitis	14
Subphrenic abscess	4
Pelvic abscess	4
Puerperal sepsis	4
Septicaemia	3
Infective endocarditis	2
Infected burns	2
Miscellaneous	11
Total	194

dangerously severe—haemoglobin less than 25 per cent.; (b) when anaemia is pronounced, though not as extreme as above, but the case is complicated by some emergency such as an unavoidable major operation, etc.; (c) when the patient's recovery must be expedited for special reasons.

2. *When haemopoietic remedies have been found to be absolutely or relatively ineffective.*—(a) Aplastic anaemia and allied states; (b) anaemia in septic and infective conditions.

In passing, it should be noted that whenever transfusion is practised for the relief of anaemia the blood used should be as fresh as possible because the red cells of blood conserved for more than a week by present methods do not last long in the recipient (Schaefer and Wiener, 1939; Kolmer, 1939; Whitby *et al.*, 1940). When fresh blood is transfused the cells slowly disappear, but are not all gone for several weeks (Ashby, 1919, 1919–20, 1921; Wearn, Warren, and Ames, 1922; Wiener, 1934; Schiödt, 1938; Dekkers, 1939).

Relation of Adequacy of Volume to Benefit

A pint transfusion can only augment the haemoglobin concentration of an adult by approximately 10 per cent. In our view, if transfusion is necessary at all, a greater increase is usually desirable, and its magnitude should be prescribed. The question will be discussed under separate headings relating to the indications which have been specified:

1a. *Dangerously Severe Anaemia.*—When a patient's haemoglobin concentration is below 25 per cent. life is in danger. The average haemoglobin level of the thirty-two patients in this group in our series (see Table I) was 21 per cent. All were in very poor condition. Fourteen appeared moribund and eleven had signs of cardiac failure. For such patients transfusion is an urgent necessity, and must often precede complete diagnosis. Exhausting special investigations, such as barium meals and enemas or various forms of endoscopy, should be regarded as out of the question until the general condition has been improved. The essential purpose of transfusion in anaemia so severe is to raise the haemoglobin to a safe level. Perhaps 35 per cent. might be regarded as safe, but it is suggested that once a slow transfusion has been started it should be continued until a really adequate margin of safety has been attained—that is, not less than 45 per cent. The patient then becomes treatable with haemopoietic remedies or enters one of the remaining categories in regard to further transfusion. The average rise of haemoglobin produced in our thirty-two patients was 41 per cent., giving an average final haemoglobin of 62 per cent. The average volume and duration of the twenty-nine transfusions to adults were 2,400 c.cm. and thirty-eight hours. All the patients except four were improved, and many were greatly improved, so that investigations and further treatment could be carried out with safety. As the transfusions proceeded it was possible to watch the continuous improvement in the patients parallel with their rising haemoglobins. It was easily seen that in most cases safety was not attained after a single pint. The only patient who showed ill effects will be mentioned later. Three of the moribund cases (leukaemia, carcinoma of stomach, lobar pneumonia, before days of sulphapyridine, in an advanced pernicious anaemia) showed neither benefit nor harm.

1b. *Anaemia Complicated by Some Emergency.*—Patients in this group (see Table I) have severe or moderate anaemia, but it is not so extreme as immediately to endanger life. Their haemoglobin concentrations are somewhere between 25 and 60 per cent. In the sixty cases of our series the average was 43 per cent. Such a degree of anaemia may considerably increase the dangers of an emergency such as a major operation.

The purpose of transfusion is rapidly to change such poor risks into better ones. This is best achieved by raising

the haemoglobin level to at least the lower limits of normality—that is, to 80 per cent. In our sixty cases the average haemoglobin concentration at the end of transfusion was exactly 80 per cent.—a rise of 37 per cent. The average transfusion to the fifty-nine adults was 2,050 c.cm. of blood during twenty-five hours. The benefit to every patient was very striking.

It is impossible with such a small and diverse series to prove statistically that risks were diminished, but there seemed no doubt about it. Some of the operation cases could hardly have been tackled prior to the use of transfusion, and none could have safely suffered much haemorrhage. Yet all withstood their operations well. Pre-operative massive transfusion to relieve anaemia has an important potentiality in regard to war casualties, many of whom may require operations when the combined effects of bleeding and sepsis have rendered them anaemic.

1c. *Anaemia in Patients Whose Recovery is Urgent for Special Reasons.*—In peacetime this indication for transfusion is of little importance, but in war it might bulk more largely, particularly in regard to accelerating the return to duty of valuable military or civil executives or technicians. In our series there was only one patient within this group—a man whose haemoglobin had fallen to 35 per cent. from chronic bleeding due to piles and for whom almost immediate return to full work was a matter of great personal importance. His piles were injected, and his haemoglobin was raised by transfusion to 90 per cent. by a total of 3,100 c.cm. of blood given over thirty-one hours. He was back at work within a week.

2a. *Aplastic and Allied Anaemic States.*—In such conditions (see Table I) the purpose of transfusion is to secure a haemoglobin concentration compatible with reasonable activity and happiness when it cannot be secured by the action of haemopoietic remedies. Opinions vary as to this level. Some would fix it at 60 per cent. and hope to stimulate the patient's bone marrow by preservation of a moderate anaemia. Others would aim at the complete abolition of anaemia and a haemoglobin of 80 to 100 per cent. Whatever percentage be decided upon, it is necessary to transfuse, in the first instance, enough blood to raise the haemoglobin to the chosen level. When the desired rise has been achieved the haemoglobin percentage must be maintained by further periodic transfusions. It should be restored by small transfusions, given through a needle, whenever it falls by 10 per cent. It is better to preserve the haemoglobin concentration by frequent small transfusions than to permit gross fluctuation in order to give less frequent massive ones. This recommendation is the outcome of experience. In our first paper (Marriott and Kekwick, 1935) we suggested that large transfusions should be used not only initially but also for maintenance. Our records include thirty patients of this group who between them received fifty-seven transfusions exceeding 1,000 c.cm. (see Table I) and many smaller ones. The average haemoglobin figures before and after the fifty-seven large transfusions were 44 per cent. and 75 per cent. respectively. Fifty-four of the transfusions were to adults, and the average volume transfused was 1,900 c.cm. during twenty-five and a half hours. The usual improvement in general condition commensurate with the haemoglobin rise was observed.

2b. *Anaemia in Septic and Infective Conditions.*—In septic and infective states patients may become progressively anaemic in spite of the full use of haemopoietic remedies. They are in a vicious circle in that toxæmia is the cause of the anaemia, while the anaemia diminishes the general fitness and capacity to withstand the toxæmia. Transfusion may break the circle by relieving the anaemia, and it is rational to use it to restore the haemoglobin percentage to normality. In the forty-four transfusions of this group (see Table I) the average haemoglobin percentages before and after transfusion were fifty and eighty-seven respectively. The average volume of blood transfused to the thirty-four adults was 1,900 c.cm. during twenty-four hours. All the patients showed great benefit. In ten instances the transfusion appeared to initiate a turning-point in the illness and to be responsible for ultimate recovery when downward progress had seemed certain to terminate in death. This group is one of the most satisfactory in the results

obtainable from adequate transfusion. In war, sepsis complicating mechanical injuries and burns is likely to provide many anaemic patients who might fall within this group.

Blood Volume during Massive Transfusion

The haemoglobin percentage in all our cases rose during the progress of the transfusions in proportion to the added red cells and without evident dilution from the added plasma. This phenomenon, upon which the benefit and the safety of large slow transfusions depend, is due to compensatory extrusion of plasma from the circulation. With rapid transfusion, extrusion takes place during the day or two after, until the blood volume is increased only by the volume of the added cells (Boycott and Oakley, 1934). With sufficiently slow administration extrusion occurs during transfusion (Marriott and Kekwick, 1936). Our original deduction of this fact was based upon frequent haemoglobin estimations during large drip transfusions for anaemia. Dow and Todd (1939) have confirmed it by plasma- and cell-volume estimations in five cases. They found that the plasma volume was either not increased or it was slightly diminished, while the circulating red cell volume was quantitatively increased by the cells transfused. Our observations show that practically full compensatory extrusion of plasma occurs during slow transfusion if the rate does not exceed 1 c.cm. per pound of the recipient's body weight per hour.

Calculation of Amount to be Transfused

Once the required rise of haemoglobin has been settled for any case the volume of blood in cubic centimetres needed may be calculated as follows:

$$\frac{\% \text{ Rise of Hb required}}{100} \times \text{Patient's normal blood volume in c.cm.}$$

The patient's normal blood volume may be approximately determined by allowing 40 c.cm. per pound of body weight as roughly estimated; obviously most patients needing transfusion cannot be weighed. In dealing with oedematous subjects, or the obese, the true weight, minus fluid or excess fat, should be estimated. This method of calculation serves for adults of all sizes and for children of all ages. A simpler method in dealing with adults of average size is to allow a pint (568 c.cm.) of blood for every 10 per cent. of haemoglobin rise required. As the transfusion progresses haemoglobin estimations should be made at intervals to ascertain if the practical result is tallying with the theoretical calculation.

In the interests of safety we now advise that when the required rise of haemoglobin involves transfusion of an amount of blood (exclusive of citrate) exceeding one-third of the patient's normal blood volume (that is, more than 13 c.cm. per pound of body weight) the transfusion should be divided into two parts separated by two clear days. In our early transfusions we often gave larger amounts—accounting for the magnitude of the averages in our series—without mishap. The criticism is sometimes made that very large transfusions depress haemopoiesis, as opposed to the effect of small ones (Vlados, 1937). However, we do not advocate large transfusions in any case in which red cell restoration by natural haemopoiesis can be waited for or is not ineffective.

It has been our practice, whenever possible, to use donors of the same group as the recipient. Among the 194 transfusions there were, however, nineteen in which more than 1,000 c.cm. of Group O blood was transfused to recipients of other groups (two Group AB, nine Group

A, eight Group B) without evidence of ill effects. Group O blood should not be mixed in the transfusion reservoir with blood of other groups.

Principles regarding Volume of Transfusion

The following is a summary with regard to volume in transfusion for the relief of anaemia uncomplicated by acute haemorrhage:

1. The purpose should be to achieve a prescribed rise of haemoglobin concentration.
2. The desirable rise of haemoglobin concentration is as follows: dangerously severe anaemia, to 45 per cent.; anaemia complicated by some emergency, to 80 per cent.; anaemia in patients whose recovery is urgent for special reasons, to 100 per cent.; aplastic and allied anaemic states, to 60 or 80 per cent.; anaemia in septic or infective conditions, to 100 per cent.
3. The volume of blood necessary depends upon the required rise of haemoglobin concentration and the patient's size. It may be simply calculated as explained above.
4. If a rise of more than 33 per cent. of haemoglobin concentration is desired the transfusion should be divided into two parts separated by two clear days.

Relation of Slow Rate to Safety

The danger of transfusion in an anaemic patient is that cardiac failure may result from circulatory overloading. The heart in chronic anaemia is grossly enfeebled, and the pathological changes in the myocardium are well known. Tung *et al.* (1937) have shown that severe anaemia may produce cardiac failure; their radiographs provide striking evidence of the extreme cardiac dilatation which may arise.

It may well be asked: How can massive transfusion be safe in such subjects? The answer is that it can be, if slow enough, because danger lies much more in speed of administration than in the amount transfused. Proof of this claim is best provided from experience, and this will first be cited. There are, however, reasons for it which will subsequently be enumerated.

The majority of the patients in our series were in poor, many in very poor, condition. Their haemoglobin figures and diseases (see Table I) have been given. Sixty-seven of them were over 50 years old, twenty-six being between 60 and 70 and nine over 70. Particularly feeble were the thirty-two whose haemoglobin concentrations were below 25 per cent. The average volume of blood (exclusive of citrate) given in the 177 transfusions to adults was 2,039 c.cm.; in twenty-one cases it was more than 3,000 c.cm. Yet almost all these patients showed no symptoms of cardiac embarrassment. Indeed, they reported themselves as being less short of breath after transfusion than before. This increased ease of breathing was of course mainly related to relief of anaemia, but it would not have been manifest had cardiac failure been produced. All the transfusions were given very slowly: the average duration of the 177 to adults was 27.1 hours, with an average rate of 84 c.cm. per hour (since the average volume of citrated blood was 2,285 c.cm.). In sixty-five the rate was slower than 60 c.cm. per hour.

In the whole series there were only five instances in which symptoms of distress developed (see Table II). In four they were slight and soon disappeared. It is one of the advantages of very slow administration that if cardiac failure does develop there is usually plenty of time to recognize it and to stop before the condition has become irreparable. The one fatal case would probably have been so recognized under hospital conditions: the transfusion was done in a private dwelling.

TABLE II.—Particulars of Patients who Showed Cardiac Symptoms during Transfusion

Age	Sex	Diagnosis	Hb before Transfusion	Volume of Citrated Blood in c.cm.	Time taken in Hours	Rate in c.cm. per Hour	Comments
55	F	Carcinoma of stomach	18%	2,800	22	127	Pulmonary oedema—death
67	F	Hypoplastic anaemia	25%	2,240	19	118	Owing to mischance the last 600 c.cm. was run in during 1 hour. Patient developed moderate dyspnoea and rales at bases; better within 2 hours of cessation of transfusion
46	F	Acholic jaundice	30%	3,130	26	120	Moderate dyspnoea and rales at bases; quickly better. Splenectomy successfully performed 6 hours after transfusion
33	M	Infective endocarditis	49%	1,220	15	81	Slight dyspnoea at end of transfusion, but pulse rate only 90
64	F	Hour-glass stomach	47%	2,500	31	81	No symptoms, but began auricular fibrillation at end of transfusion. Normal rhythm 2 days later

Bearing in mind the severity of the cases in our series, we are convinced that there would have been more cardiac failure had transfusion of a pint in half an hour been practised (Plummer, 1936, 1937; Pygott, 1937; Riddell, 1939). And, moreover, the benefit would only have been one-quarter of that actually secured. However, we were not satisfied that any cases of cardiac failure should have occurred, and it became our aim to formulate principles giving practically complete safety. These principles are set forth below. It will be observed that they are transgressed in the case of the five patients of Table II, all of whom were transfused in our earlier days, when we tended to use rather faster rates and larger amounts than we do now. In the last three years we have not encountered the development of cardiac failure during a drip transfusion.

Principles regarding Rate of Transfusion

The following is a summary of the principles regarding the rate of transfusion in anaemia uncomplicated by acute haemorrhage:

1. The rate should never exceed 1 c.cm. per pound of body weight per hour.
2. In subjects suffering from very severe anaemia (haemoglobin less than 25 per cent.), cachexia, or cardiac or respiratory disease, the rate of transfusion should not exceed 0.5 c.cm. per pound of body weight per hour.
3. The determined rate of flow should be maintained steadily. No acceleration, even for short periods, should be permitted.
4. Careful watch should be kept for manifestations of cardiac failure (dyspnoea, cough, basal rales), and transfusion must be suspended if they appear.

These principles should be observed whatever the volume of the transfusion—even for transfusions of 500 c.cm.

Principle 1 applied to patients weighing 12 stone and 8 stone, and a baby of 10 pounds, means respective maximal rates of 168, 112, and 10 c.cm. per hour. Principle 2 means maxima of half these amounts per hour. When slow transfusion is effected by the drip method it is necessary to translate c.cm. per hour into drops per minute. The size of drop may vary considerably in different drip bulbs. The one used should be roughly calibrated by counting the number of drops filling a small measure graduated in c.cm. Regarding Principle 3, the importance of a steady rate is illustrated by the second case in Table II. When the usual screw-clip regulator is in use flow is apt to

fluctuate, and to overcome this we have devised a special regulator which gives a reliable steady flow even at very slow rates. We shall shortly publish details of it.

The claim for the safety of very slow massive transfusion in anaemia has so far been based on the facts of experience. The reasons why it is safe are as follows:

Any extra burden is imposed upon the heart very slowly.

Extrusion of plasma causes the total blood volume to be little increased. In an adult the addition from a transfusion equivalent to a third of his normal blood volume is unlikely to be much in excess of a pint, and it may be less.

The process of red cell addition combined with plasma extrusion results in considerable increase of the oxygen-carrying power per unit-volume of blood. From this the heart itself benefits.

With very slow transfusion, other points in technique being equal, rigors are less frequent, and less severe when they do occur.

It may be suggested that time might be saved by transfusing red cells, without plasma, suspended in a minimum of isotonic non-protein fluid; or the cells might be administered in a minimum of plasma after having been allowed to sediment in the transfusion reservoir—an expedient which we have used on several occasions. However, we believe that even if red cells alone are transfused it is still not safe to increase the rate of their addition. Furthermore, there are probably nutritional and other factors present in plasma from normal donors which are of benefit to anaemic patients.

Summary

In every transfusion the volume of blood to be administered and the rate of its administration should be matters of primary importance. The custom of "giving a transfusion," meaning about a pint of blood in half an hour, is irrational and unsatisfactory.

Transfusion for the relief of anaemia uncomplicated by acute haemorrhage is particularly considered, and principles concerning volume and rate, summarized in the body of the paper, are submitted.

We wish to express our thanks to members of the honorary staff of the Middlesex Hospital for permission to include the figures relating to transfusions performed upon patients under their care.

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J. Meunier (*Thèse de Paris*, 1940, No. 129), who records fourteen illustrative cases in soldiers, states that seven days after inoculation for typhoid fever a local reaction may develop suggesting that an abscess has been caused by lack of sterilization of the needle. The symptoms rapidly subside in 24 to 48 hours. This occurrence is of military importance, and the authorities should be warned that a week after inoculation two or three times as many sick may report themselves as on ordinary occasions.