Perspective

Factoids and Critical Care

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Factoids are bits of information that are widely taught, eminently plausible, tenaciously held but are demonstrably false. They are deemed true either because they have appeared in print or because they are repeated so often that they become accepted.[1,2] There are plenty of factoids in the domain of medicine, and critical care is no exception. They are demolished only by robust studies carried out by questioning minds similar to young Alice in Intensiveland[3] that test the validity of existing urban legends in medicine. This is important because factoids are analogous to blocking antibodies —they stifle innovative thinking by blocking new ideas. They are particularly tenacious when attached to numerical values. The relationship between an intensivist and monitored parameters in the intensive care unit (ICU) has been compared to a princess kissing several frogs[4] with the hope that one of them would morph into a prince and save the patient's life and the intensivist's reputation!

Two recent publications in the *New England Journal of Medicine* deal with factoids in critical care—the first (TRISS) studied the transfusion trigger level for haemoglobin in critically ill patients with septic shock[5] and the second (CALORIES)[6] evaluated the route of early feeding in critically ill patients.

In the mid-1970s, Alvan Feinstein coined the phrase 'The Curse of Kelvin'[7]—referring to the unthinking and inappropriate worship of quantifiable information in medicine. The 'appropriate' haemoglobin level was one such number. The classical trigger for transfusion depended on the 10/30 rule (the first referring to the haemoglobin value and the second to the corresponding haematocrit). In 1982, Allen and Allen[8] suggested the 10/30 rule as a clinically useful trigger for transfusing blood. Although the 10/30 rule was derived from perioperative patient studies and was physiologically logical.[9] Intensivists adopted it enthusiastically because the daily measurement of plasma haemoglobin was a cheap and simple investigation. In addition, the number 10 was an easy number to remember and use as it simplified oxygen kinetic calculations! Nevertheless, the 10/30 rule as a transfusion trigger in the critically ill was never supported by a randomized controlled trial. Its use was strengthened by the Early Goal Directed Therapy (EGDT) study[10] in which a bundled approach to the management of septic shock resulted in an improved outcome. One of the components of EGDT was to ensure a haematocrit of 30% by transfusion if the central venous oxygen saturation was <70%. The effect of transfusion was not analysed separately in the EGDT study as it was meant to assess the bundle as a whole and not its component strands. This number was then reinforced by the Surviving Sepsis Campaign guidelines which recommended a target haemoglobin level of 10 g/dl during initial resuscitation but a reduced transfusion threshold of 7 g/dl after stabilization.[11]

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Several new studies (TRICC,[12] FOCUS,[13] RELIEVE[14]) as well as a meta-analysis (Cochrane database[15]) have shown that the transfusion trigger could be lower in the critically ill. TRISS may be the last nail in the coffin of a liberal transfusion strategy. The study is an international, multicentric, partially blinded, randomized trial including adults (≥18 years) admitted with septic shock. Two groups (503 *v*. 497) of patients were compared. One group followed a restrictive transfusion policy (transfusion trigger of 7 g/dl) and the other a more liberal transfusion policy with a higher transfusion threshold of 9 g/dl. The trial protocol was pragmatic in that routine ICU care was not altered except for the haemoglobin threshold for transfusion. Leukoreduced red cells were used. No significant difference in mortality was found at 90 days between the two groups (43% in the lower threshold group *v*. 45% in the higher threshold group). There was also no difference in secondary outcome measures: use of life support (defined as use of mechanical ventilation, inotropes/vasoactive agents or renal replacement therapy) at 5, 14 and 28 days after randomization, numbers of patients with ischaemic (cerebral, myocardial, intestinal or limb) events or severe adverse reactions (allergic reaction, haemolysis, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload [TACO]) or in the percentage of days alive and out of hospital in the 90 days post-randomization. Subgroup analysis (chronic cardiovascular disease, older age, greater disease severity) did not show any significant difference either. In the low threshold group, 36% of patients did not need transfusion compared to 1% in the high threshold group. In addition, the low threshold group received 50% fewer units of blood. The limitations of the study were that it did not assess the occurrence of silent cerebral ischaemic events and that it excluded patients with acute myocardial infarction.

Blood is the fluid that transports oxygen and nutrients, removes waste, protects tissues and initiates repair. However, transfused blood can also be the trigger for adverse events such as TRALI, TACO and TRIM (transfusion-related immunomodulation) as well as infections, and allergic, febrile and haemolytic reactions. Stored blood is also qualitatively inferior to fresh blood.[9] It has lower amounts of ATP in red blood cells (shift of Hb-O_2 dissociation curve to the left resulting in tighter binding of oxygen and less release to tissues), higher potassium levels, higher levels of pro-inflammatory mediators and is 'rheologically challenged' (less supple, hence its transit through the microcirculation is impaired). A combination of these factors may explain the lack of expected benefit from transfusing blood to maintain a higher haematocrit in the critically ill. In India, this study has important economic implications as blood is expensive and its supply is insufficient. It is economically good news for patients, blood banks and ICUs as this inadequate resource can be utilized elsewhere.

The second study[6] examined whether the route of nutrition (parenteral *v*. enteral) altered the outcome of critically ill adults (≥18 years of age). It was based on the assumption that early

nutrition would be beneficial for critically ill patients and the study examined whether the parenteral route for nutritional support was more effective than the enteral route under usual conditions. It was an open, multicentre, randomized controlled trial. Early feeding was started within 36 hours of admission to achieve the target calorie goal of 25 kcal/kg (this included non-nutritional calorie sources such as propofol) within 48–72 hours and continued for 5 days. Protein/amino acid targets were based on local practice. Glycaemic control was maintained at <180 mg/dl. There was no significant difference in the primary outcome (mortality at 30 days) between the two groups (33.1% died in the parenteral group and 34.2% in the enteral group). Hypoglycaemia and vomiting, unsurprisingly, were significantly less frequent in the parenteral group but there were no differences in any of the other secondary outcomes within 90 days (duration of organ support, infectious and other complications, length of stay in ICU/hospital and duration of survival). Neither group achieved target calorie goals–an unexpected result considering that medical personnel administered the parenteral nutrition. This was explained by the investigators as being due to lack of availability of the nutritional product, delays or interruptions in delivery due to procedures, transfers and other practical and organizational roadblocks. It is important to note that this result differs from a previous meta-analysis[16] and a recent study[17] in that infections were not increased in the parenteral group. This could be attributed to a better implementation of infection control bundles or to the fact that patients did not achieve caloric goals. There is evidence that providing about 70% of estimated energy results in the best outcome because an increased dose of parenteral nutrition may contribute to the increase in infectious complications.[18] The inadvertent underfeeding in this trial could have had a beneficial protective effect!

The limitation of this contextual study is that it is not externally valid for us in India as it was done within a system with much more financial resources. It is reassuring to note that the mortality was the same in both the groups and this study cannot be used as a fulcrum to push for parenteral nutrition in critically ill patients thereby increasing the financial burden. However, one important issue in this study can be solved by focused trials in India. The degree of malnutrition was similar but low in both groups in the trial (about 8% of patients in both groups were malnourished). In India, the percentage of patients with malnutrition could be higher and therefore early feeding could result in a better outcome. If early nutrition is given to a group of patients who do not need it, it is likely that no change can be shown in the outcome irrespective of the route of administration. These questions can be answered with more contextual studies in Indian ICUs that are likely to have a higher prevalence of malnutrition.

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