Practical Applications of Intravenous Fluids in Surgical Patients

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Reprint

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Contents

Chapter 4

Pharmacology of Colloids

Colloids are large molecular weight (nominally Mw > 30,000), homogenous, non-crystalline substances that largely remain in the intravascular compartment. Colloids are important in capillary fluid dynamics because they are the only constituents which are effective at exerting an osmotic force across the wall of the capillaries. However, a colloid loses this property, when capillary membranes are altered in a diseased state.

In normal plasma, the plasma proteins are the major colloids present. Albumin solutions are available for use as colloids. In addition, various other solutions containing artificial colloids are available. Most colloid solutions contain colloid molecules dissolved in isotonic saline. In addition to the above, colloid molecules dissolved in isotonic dextrose, hypertonic saline and isotonic balanced or physiological electrolyte solutions are also available.

General characteristics of colloids

Colloids have certain general characteristics which determine their behaviour in the intravascular compartment. These characteristics are explained as follows:

1. Molecular Weight (MW)

Two molecular weights are quoted for colloid solutions. They are:

a. Mw: Weight average molecular weight
b. Mn: Number average molecular weight

a. Mw: Weight average molecular weight
   It's based on the fact that a bigger molecule contains more of the total mass of the polymer sample than the smaller molecules. The probability factor in a weight average molecular weight emphasises the mass of the molecules so that the heavier molecules are more important.

   Molecular weight measurements that depend on the contributions of molecules according to their mass give weight-average molecular weights. The Mw determines viscosity.

b. Mn: Number average molecular weight
The number average is simple arithmetic mean. It is just the total weight of all the polymer molecules in a sample, divided by the total number of polymer molecules in a sample. Mn determines the oncotic or osmotic pressure.

2. Colloid Molecular Size (Fig. 4.1)

In physical and organic chemistry, the dispersity is a measure of the heterogeneity of sizes of molecules or particles in a mixture. Colloidal molecular size can be highly variable.

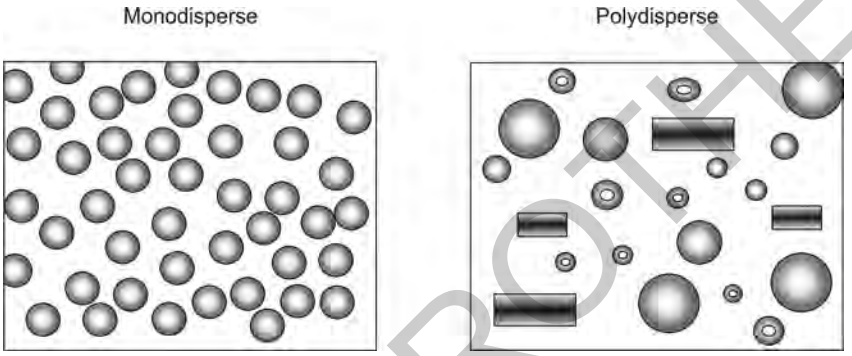

Figure 4.1: Colloid molecular size

a. Monodisperse
A collection of objects is called monodisperse if the objects have the same size, shape or mass. Albumin is said to be monodisperse because all molecules have the same molecular weight (so Mw = Mn).

b. Polydisperse
A sample of objects that have an inconsistent size, shape and mass distribution is called polydisperse. The objects can be in any form of chemical dispersion such as particles in a colloid, droplets in cloud, or polymer molecules in a solvent. Artificial colloids and the various preparations of plasma proteins in solution (plasma protein fraction, fresh frozen plasma) are all polydisperse with molecules of a range of molecular weights.

Gelatins have the smallest molecular weight, whereas hydroxyethyl starch solutions have the highest, accounting for their different intravascular persistence.

3. Plasma Volume Expansion

The degree of volume expansion is mainly determined by the molecular weight, whereas the intravascular persistence is determined by the elimination of the colloid. The potency of colloid fluids as plasma volume expander is related to the colloid osmotic pressure exerted by each fluid.

Plasma volume expanders increase the oncotic pressure in the intravascular space. Water moves from the interstitial spaces into the intravascular space, increasing the circulating blood volume. This increased volume leads to an increase in central venous pressure, cardiac output, stroke volume, blood pressure, urinary output and capillary perfusion, and a decrease in heart rate, peripheral resistance and blood viscosity.

Colloid solutions generally are administered in a volume equivalent to the lost plasma volume. When compared to crystalloids, colloids induce a greater plasma volume expansion for the same administered volume.

The duration of volume expansion varies, however, among the different colloids, gelatins have the shortest duration of volume expansion.

4. Osmolality

Almost all colloid solutions have a normal osmolality.

5. Colloid Osmotic Pressure (COP) (Fig. 4.2)

The oncocity of the solution will influence the vascular expansion. The higher the oncotic pressure, the greater the initial volume expansion. The proteins in plasma do not pass through the capillary membrane of the vascular compartment. These proteins are responsible for the effective osmotic pressure between the vascular and interstitial fluid compartments. This is also referred as colloid osmotic pressure. Colloid osmotic pressure is also produced by large molecules which are present in colloidal solutions, e.g. Albumin, Hetastarch, and Dextran.

1. This force (colloid osmotic pressure or oncotic pressure) opposes hydrostatic pressure (which favours the movement of water out of a fluid compartment). A colloid with a large number of small molecules will have a short duration of action as these leak out of the circulation.

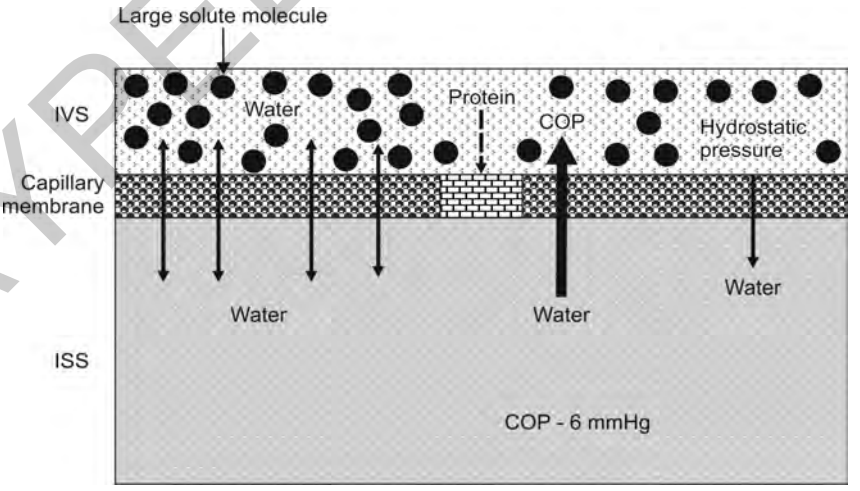

Figure 4.2: Importance of colloid osmotic pressure

2. A colloid with a large number of large molecules will have a longer duration of action as these remain in the circulation for a longer time.
3. The ability of each fluid to expand the plasma volume is directly related to the COP. The oncotic pressure can be expressed as water binding capacity.

6. Plasma Half-life

The plasma half-life of a colloid varies greatly and depends on its molecular weight, the elimination route (mainly eliminated by the renal route).

7. Electrolyte Content

Sodium concentration is low in 'salt –poor albumin' (25% Albumin). However, it is to be noted that, the sodium content of other commercially available colloid solutions is similar to that of crystalloid solutions, while the potassium concentration differs.

Urea-linked gelatin solutions contain a small, but not negligible, concentration of potassium and calcium. In case of succinylated linked gelatin solutions, the concentration of potassium and calcium is negligible.

8. Acid-base Composition

Albumin and gelatin solutions have physiological pH, while other solutions tend to have acidic pH.

Plasma Substitutes

1. Those designed to provide colloid osmotic pressure or expand the plasma volume, i.e. colloid and crystalloid.
2. Those able to transport oxygen, i.e. perfluoro–compounds and encapsulated haemoglobin.

Types of colloidal plasma substitutes

I. Naturally occurring plasma derivative
   1. Human albumin solutions
      a. 5% Albumin
      b. 25% Albumin
   2. Plasma protein fraction (PPF)
   3. Fresh frozen plasma
   4. Immunoglobulin solution

II. Semisynthetic colloid
   1. Dextran
      a. 10% Dextran 40 in 0.9% Saline
      b. 6% Dextran 40 in 5% Dextrose
      c. 6% Dextran 70 in 5% Dextrose
   2. Gelatin
      a. Urea-cross linked gelatins
         - Polygeline 'Haemaccel', Hoechst

b. Succinylated or modified fluid gelatins (MFGs)
   - Gelofusine
   - Plasmagel
   - Plasmion

c. Oxypolygelatins
   - Gelifundol

3. Hydroxyethyl starches (HES)
   a. 1st generation—Hetastarch
      - 450/0.7—Hestar-450 (0.9% Saline)
      - 600/0.7—6% Hespan or Hetaspan (0.9% Saline)
      - 600/0.7—6% Hextend (Ringer's lactate)

   b. 2nd generation—Pentastarch
      - 3% HES—200/0.5—Steril
      - 6% HES—200/0.7—Steril
      - 10% HES—200/0.7—Steril

   c. 3rd generation—Tetrastarch
      - 6% HES 130/0.4—Voluven in normal saline
      - 6% HES 130/0.4—Volulyte in an isotonic electrolyte solution

Functions of colloid plasma substitutes

Colloidal plasma substitutes need to provide essential functions of plasma proteins. They have colloid particles giving rise to colloid osmotic or oncotic pressure, which can be expressed as water binding capacity in comparison with crystalline solution. Colloidal plasma substitutes are impermeable to the capillary or glomerular membrane.

Whereas, isotonic solution confine to the ECF, iso-oncotic solutions confine to the IVS, thereby making colloid solutions ideal for replacing intravascular deficit.

Indications of colloids

1. Emergency treatment of shock especially due to the loss of plasma.
2. Conditions associated with large protein losses such as acute management of burns.
3. Clinical situations of hypo-albuminaemia:
   - Following paracentesis
   - Patients with liver cirrhosis (for extracorporeal albumin dialysis—ECAD)
   - After liver transplantation
   - Fluid resuscitation, especially in severe fluid deficits (e.g. haemorrhagic shock) prior to blood availability for transfusion.
   - In conjunction with crystalloids if fluid load exceeds 3-4 L prior to transfusion.

- Fluid boluses in critically ill patients, where volume is critical and crystalloids use would be excessive, e.g. ICU, pulmonary oedema, congestive cardiac failure, renal conditions, etc.

Human albumin

General Properties

Albumin is the principle natural colloid comprising 50-60% of all plasma proteins. It contributes to 80% of the normal oncotic pressure of plasma in healthy individuals.

Albumin consists of a single polypeptide chain of 585 amino acids with a molecular weight of 69,000 dalton. Albumin has ellipsoid molecules, which are non-viscous, and very flexible in nature, thereby helping in the preservation of the structure of red blood corpuscle.

Albumin Synthesis

Albumin synthesis is influenced by normal nutritional status of the patient and depends on availability of adequate amino acids and calories. Hormonal environment, e.g. growth hormone, adreno-corticotropic hormones, insulin, testosterone also play an important role in albumin synthesis.

30% of total albumin is synthesised in the liver which can compensate 2-5 times loss of albumin. The inflammatory cytokines, e.g. tumour necrosis factor (TNF), interleukin 6 (IL-6), reduce the availability of albumin messenger ribonucleic acid (RNA) and thereby decreases the albumin synthesis in patients with inflammatory states.

Shelf-life and Storage

Shelf-life depends on the storage temperature:

Temperature	Shelf-life
Room temperature (20–25°C)	3 years
2–8° C	5 years
After opening vial	4 hours

Types of Albumin

The commercially available preparation is a heat-treated preparation of human serum albumin. All albumin preparations including PPF are heated to 60° C for 10 hours to inactivate viruses like hepatitis viruses and HIV. There are two types of human serum albumin, 5% Albumin and 25% Albumin.

1. **5% Albumin solution (50 gm/L or 5 mg/100 ml)**
   5% Albumin (human) is a sterile, liquid preparation of albumin derived from large pools of human plasma. Albumin (human) 5% contains no preservative, is a clear to yellow or green coloured, viscous liquid.

The composition of Albumin (Human) 5% is as follows:

Component	Quantity 1000 ml
Protein, of which ≥96% is human albumin	50 gm
Sodium	130-160 mmol/L
Potassium	≤ 2 mmol/L
N-acetyl-DL-tryptophan	0.064-0.096 mmol/gm protein
Caprylic acid	0.064-0.096 mmol/gm protein
Water for injections	1000 ml

5% Albumin is equivalent volume for volume to normal human plasma. When administered intravenously to an adequately hydrated patient, the oncotic (colloid osmotic) effect of 5% Albumin is to expand the circulating blood volume by an amount approximately equal to the volume infused. Albumin is responsible for 70-80% of the colloid osmotic pressure of normal plasma, thus making it useful in regulating the volume of circulatory blood. The degree and duration of volume expansion depends upon the initial blood volume.

Albumin stabilises circulating blood volume. When treating patients with diminished blood volume, the effect of infused albumin may persist for many hours. The haemodilution lasts for a shorter time when albumin is administered to individuals with normal blood volume.

Albumin is distributed throughout the extracellular compartments. More than 60% of the body albumin pool is located in the extravascular fluid compartment.

- 5% solution is iso-oncotic and leads to 80% initial volume expansion which lasts for 12-18 hours whereas 25% solution is hyperoncotic and leads to 200-400% increase in volume within 30 minutes. This effect persists for 16-24 hours.
- 5% Albumin or plasma protein fractions (plasmanate) have a colloid osmotic pressure of about 20 mmHg (i.e. near normal colloid osmotic pressure of plasma).
- The total body albumin in a 70 kg man is estimated to be 350 gm, it has a half-life of about 13-19 days with a turnover of approximately 15 gm per day.

It is primarily used in treatment of shock associated with surgery, haemorrhage, trauma, burns, renal failure and cardiovascular collapse.

2. 25% Albumin (250 gm/L or 25gm/dl)

- This contains 96% albumin and 4% globulin. It is diluted to 5% solution in electrolyte before infusion. Mostly it is available in 100 ml vials.
- Some preparations are salt poor albumin.
- A colloid solution of 25% Albumin contains purified albumin at five times the normal concentration.

- When administered, it has the potential to expand the plasma volume by four to five times the volume provided.
- It has a colloid osmotic pressure of 70 mm Hg.
- It is selected when the current plasma volume is diminished, but blood pressure is acceptable and the total extracellular fluid compartment is expanded.

3 . Plasma protein fraction (PPF)

- It is available as 5% solution in electrolytes and contains 83% albumin and 17% alpha and beta globulins.
- All albumin preparations including PPF are heated to 60° C for 10 hours to inactivate viruses like hepatitis viruses and HIV.

Functions of albumin in health

1. Colloidal Osmotic Pressure

Albumin exerts colloid osmotic or oncotic effect at the level of the capillaries.

2. Coagulation

Albumin influences coagulation by decreasing platelet aggregation and heparin like activity. It contributes to the formation of the normal anion gap influencing the acid base status. Although controversial, there is evidence that albumin might influence the microcirculation by modifying capillary permeability.

3. Transport of Compounds

Many endogenous and exogenous compounds are transported by albumin in the blood, e.g. calcium and magnesium. Albumin also carries bilirubin, fatty acids, steroid, vitamin D and thyroxin.

For drugs that strongly bind to albumin, and those with a narrow therapeutic range, hypo-albuminaemia will increase free fraction of the drug. The increased free fraction of the drugs can lead to toxicity by enhancing their action, e.g. warfarin, phenytoin, while some drugs could lead to beneficial effects such as ceftriaxone.

Metabolism

1. Albumin is synthesised only in the liver and has a half-life of approximately 20 days. After synthesis, albumin is not stored but secreted into the blood with 42% remaining in the intravascular compartment.
2. In health, albumin synthesis matches albumin metabolism. The liver has a limited capacity to increase albumin synthesis. Thus, in case there is increased catabolism or loss, such as renal loss in nephrotic syndrome or gastrointestinal loss in protein losing enteropathy, the body is unable to maintain a normal plasma concentration of albumin. Certain disease states such as sepsis, liver disease, trauma and fasting results in reduced albumin.

Albumin in critical illnesses

1. Albumin as a prognostic marker
   Although albumin has been found to be a prognostic marker in critical illnesses, it's functioning in case of diseases is not clear.

   In critically ill patients, survivors have a higher serum albumin concentration than non-survivors. Hypoalbuminaemia is a dose dependent predictor of poor outcome. Each 1 gm/dl decrease in serum albumin increases the chances of mortality.

   In hospitalised patients, low serum albumin is associated with prolonged ICU stay by 28%, higher mortality, morbidity 89%, and a higher complication rate. These are independent of patient's nutritional status and inflammatory status.

   The national veterans administration Surgical Risk Study of 54,215 major non-cardiac surgery cases indicates that the preoperative serum albumin concentrations have been the strongest predictor of surgical mortality and morbidity.
2. The value of albumin replacement
   The value of albumin replacement is unclear. Thus, the effect of albumin on mortality illnesses remains debated. In children, an improvement in the absorption of food has been seen when hypoalbuminaemia has been corrected. This is considered to be a result of the reduction in bowel oedema.

   In neonates, albumin has been used to treat hypotension, metabolic acidosis and promote diuresis. Unfortunately several of these studies are small scale and some of these effects may also be achieved with other agents that are both, more effective and cheaper.
3. Possible reasons why albumin is ineffective in following conditions:
   - Patients with septic shock
     In septic shock, the release of inflammatory mediators results in an increase in the leakiness of the vascular endothelium. The administration of exogenous albumin does not treat the damaged endothelial membrane. Indeed, it may compound the problem by adding to the interstitial oedema.
   - Patients with hypoalbuminaemia
     The way in which individuals with hypoalbuminaemia adapt to a low albumin state is unknown, but may be of relevance in cases of acute hypoalbuminaemia seen in critical illness.
   - Patients with increased catabolism
     Catabolism increases in a diseased state in patients with increased catabolism. Again, the administration of exogenous albumin does not treat the cause of the problem and therefore might not benefit.

Indications for the infusion of albumin

The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient, based on official recommendations. These

solutions are chosen when crystalloids fail to sustain plasma volume for more than a few minutes because of low colloid osmotic pressure of plasma.

1. Emergency treatment of hypovolaemic shock
   - 5% Albumin is iso-oncotic with normal plasma and on intravenous infusion will expand the circulating blood volume by an amount approximately equal to the volume infused.
   - In condition associated mainly with a volume deficit, albumin is best administered as 5% solution, but where there is oncotic deficit, Albumin 25% is preferred. This is also an important consideration where the treatment of the shock state has been delayed. If 25% Albumin is used, appropriate additional crystalloid should be administered.
   - Crystalloid solutions in volumes several times greater than that of 5% Albumin may be effective in treating shock in younger individuals who have no pre-existing illness at the time of incident. Older patients, especially those with pre-existing debilitating conditions or those in whom the shock is caused by medical disorder or where the state of shock has existed for sometime before active therapy could be instituted, may not tolerate hypoalbuminaemia as well.
2. Burn therapy
   An optimal therapeutic regime with respect to the colloids, crystalloids and water following extensive burns has not been established. During the first 24 hours after sustaining thermal injury, large volumes of crystalloids are infused to restore the depleted extracellular fluid volume.
   Beyond 24 hours, albumin can be used to maintain plasma colloid osmotic pressure. 25% Albumin is preferred for this purpose. Albumin is administered to maintain the albumin level of 5.2 gm/100 ml.
3. Acute liver failure
   In the uncommon situation of rapid loss of liver function, with or without coma, administration of albumin may serve the double purpose of supporting the colloid osmotic pressure of plasma as well as binding excess plasma bilirubin.
4. Sequestration of protein rich fluids
   This occurs in condition such as acute peritonitis, pancreatitis, mediastinitis and extensive cellulitis. The magnitude of loss into the third space may require treatment of reduced volume or oncotic activity with an infusion of albumin.
   5% Albumin is most appropriately used when there is abnormal loss of proteins from the vascular space.
5. Cardiopulmonary bypass
   With the relatively small priming volume required with modern pump, pre-operative dilution of blood using albumin and crystalloid has been shown to be safe and well tolerated. Although the limit to which the haematocrit and plasma protein concentration can be safely lowered has not been defined, it is common practice to adjust the albumin and

crystalloid pump prime to achieve a haematocrit of 20% and a plasma albumin concentration of 2.5 gm per 100 ml in the patient.

6. Others
   - Albumin is a transport protein and it may be useful in severe jaundice in haemolytic disease of the newborn.
   - Removal of ascitic fluid from a patient with cirrhosis may cause changes in cardiovascular function and even result in hypovolaemic shock. In such circumstances, the use of albumin infusion may be required to support blood volume.
   - Immunoglobulin deficiencies.
   - Plasma cholinesterase deficiencies.
   - Albumin is used as an exchange fluid to replace removed plasma in therapeutic plasmapheresis.
7. The use of a bottle of albumin concurrently with a diuretic to decrease peripheral oedema and improve urine output in patients with anasarca is under scrutiny.
   Possible future roles include utilising albumin for its potential free radical scavenging.

Contraindications

1. Hypersensitivity to albumin preparations or to any of the excipients.
2. In chronic nephrosis, infused albumin is promptly excreted by the kidneys with no relief of the chronic oedema or effect on the underlying renal lesion.
3. Similarly, in hypoproteinaemic states associated with chronic cirrhosis, malabsorption, pancreatic insufficiency and undernutrition, the infusion of albumin as a source of protein is not justified.
4. Certain patients, e.g. those with a history of congestive cardiac failure, renal insufficiency or stabilised chronic anaemia, are at special risk of developing circulating overload.

Side Effects

1. Adverse effects of albumin infusion are rare. These include nausea, vomiting, and allergic reaction including anaphylactic shock. The incidence of anaphylactoid, anaphylaxis reactions are 0.003 to 1.53%.
2. Circulatory overload.
3. Febrile reaction.
4. Hypotension due to vasoactive substances from plasma . Sometime it is seen with PPF when the rate of administration is more than 10 ml/min.

Precautions and Safety

1. Do not use solutions of Albumin (human) 5% which are cloudy or have deposits. Once the infusion container has been opened, the content should be used immediately.
2. Discard unused portion. Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients.

3. 20-25% human albumin solutions are relatively low in electrolytes compared to the 4-5% human albumin solutions. When albumin is given the electrolyte status of the patient should be monitored and appropriate steps taken to restore or maintain the electrolyte balance.
4. The plasma volume expansion is at the cost of an interstitial fluid shift. Hence, 20% Albumin should not be used for volume resuscitation in patients with hypovolaemia (fluid deficit), unless these patients are treated with crystalloid plasma substitute.
5. If comparatively large volumes are to be replaced, controls of coagulation and haematocrit are necessary. Care must be taken to ensure adequate substitution of other blood constituents (coagulation factors, electrolytes, platelets and erythrocytes).
6. Albumin should not be used for parenteral nutrition. In patients with severe anaemia or cardiac failure, albumin is contraindicated. However, it can be given with caution in patients with cardiac insufficiency or low cardiac reserve.
7. Albumin infusion increases circulatory volume if fast infusion is given. Hypervolaemia may occur if the dosage and rate of infusion are not adjusted to the patient's circulatory situation. At the first clinical sign of cardiovascular overload for example, headache, dyspnoea, jugular vein congestion or increased blood pressure, raised venous pressure and pulmonary oedema, the infusion is to be stopped immediately.

Advantages

1. Natural colloid
   As albumin is a natural colloid it is associated with lesser side-effects like pruritus, anaphylactoid reactions and coagulation abnormalities compared to synthetic colloids.
2. Degree of volume expansion
   25% Albumin has a greater degree of volume expansion as compared to rest of colloids. 5% Albumin solution has a similar degree of volume expansion as compared to hetastarch but greater than gelatins and dextrans.
3. Other benefits
   Albumin acts a principal binding protein of endogenous and exogenous substances. It also possesses antioxidant and scavenging effects. Albumin being negatively charged protein contributes to the formation of normal anion gap, influencing the acid-base status.

Disadvantages

1. Cost effectiveness
   Albumin is expensive as compared to synthetic colloids.
2. Volume overload
   In septic shock the release of inflammatory mediators has been implicated in increasing the 'leakiness' of the vascular endothelium.

Practical Applications of
Intravenous Fluids
in Surgical Patients

Salient Features

- Includes the fundamentals of body fluid balance
- Detailed discussion of all the commonly used intravenous fluids
- Compact and yet detailed practical approach to fluid therapy in various surgical conditions
- Wide array of self-explanatory figures
- Language used is lucid and easy to understand
- Conveys the knowledge in a simplified and systematic manner
- Serves as a good teaching guide to the advanced users, too.

Shaila Shodhan Kamat is the Professor and Head, Department of Anaesthesiology and ICU, Goa Medical College, Goa, India, an alumnus of the same alma mater. Her research papers are published in various acclaimed journals. She has been chosen as a National Faculty to conduct workshops on mechanical ventilation, in India, by the Hamilton Medical Academic Education and Research, Switzerland, and the Society for Board of Control of Life Support Courses, Erode, Tamil Nadu, India, considering her rich clinical and teaching experience of more than 30 years in the field. Her areas of special interest include paediatric anaesthesia, airway management, postoperative pain management and mechanical ventilation. Apart from being an anaesthesiologist, a teacher and an author of the much-acclaimed book Practical Applications of Mechanical Ventilation, she is an articulate and multifaceted person having passionate interest in many traits.

Reviews

Dr Shaila Kamat has been my teacher and continues to be one. The most amazing aspect is the energy and enthusiasm, she has brought into everything she has done–teaching, giving presentations in national conferences, writing books, administration and art. I am happy to know that reprint of her book is being published and I wish her all the success for the present one and many more that are awaited from her pen.

—Dr Prasad K Kulkarni
Professor, Anaesthesiology
MVJ Medical College and Research Hospital
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In this fast-evolving field of medical science, to keep abreast with the latest developments is difficult. But, to learn and master it with interest and passion, for teaching needs special mention. Dr Shaila Shodhan Kamat's knowledge, skills and her passion, for teaching placed her on a unique pedestal, amongst many excellent teachers. The basics of anaesthesia and intensive care taught by her, have been a strong foundation for me in my career.

—Dr Rajkumar Chandran
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The phrase "No man can be a good teacher unless he has feelings of warm affection towards his pupils and a genuine desire to impart to them what he believes to be of value", very aptly describes Dr Shaila Shodhan Kamat. She has always inspired me with her perseverance, dedication and commitment towards her work. This book will be reliable source of information to her students and readers for the years to come.

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