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Unravelling Basic Concepts in Perioperative Pharmacology.

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ABSTRACT

Ideal perioperative management of surgical patients requires proper and complete knowledge of the various drugs used in the preoperative, intraoperative and postoperative period. This includes pharmacological knowledge of the different general anaesthetics, local anaesthetics, neuromuscular blocking drugs, empirical antibiotics, intravenous fluids, and various chronic drug therapy that the surgical patient might be on. The concepts underlying the use of these drugs in the perioperative period are vast and interesting. A proper understanding of these concepts will bring about a better perioperative outcome for the surgical candidate.

Keywords: Anaesthesia, Surgery, Nitrous oxide, Halothane, Propofol, Lignocaine

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INTRODUCTION

Perioperative period, technically the period in and around the surgical operation, is broadly divided into three phases: preoperative, intraoperative and postoperative phases. Preoperative phase is the time period from the point of admission of the surgical candidate to the point of the first surgical incision placed by the surgeon (sometimes, till the patient is taken into the operating room). Intraoperative phase includes the actual duration of the surgical procedure in the operating room (OR). Postoperative phase begins when the patient is shifted out of the OR till the time point of recovery, which varies from procedure to procedure and between individuals [1].

It is estimated that there are around 234 million surgeries being performed annually around the world (statistics from 2008). Of these, around 7 million patients are subjected to one complication or the other. Around 1 million deaths are said to occur solely due to perioperative complications [2]. All surgical procedures pose varying amounts of stress on the surgeon, the anaesthetist as well as on the surgical patient. Most of the drugs that are used in the perioperative period find minimal use at other time points. This makes the understanding of the pharmacology of these drug classes even more essential, so as to prevent perioperative morbidity and mortality.

The major drug groups that are used in the perioperative period include pre-anaesthetic medication, anaesthetic agents and neuromuscular blockers. Further, management of any chronic medication that the surgical candidate has been on is also of utmost importance. This comprehensive review, divided into five sections (Preanaesthetic medication, General anaesthetics, Local anaesthetics, Neuromuscular blocking agents and Management of chronic medication), has been designed to give an overview of the various concepts involved in perioperative drug utilization and management. Information on empirical antibiotic usage and intravenous fluids are beyond the scope of this review article.

PRE-ANAESTHETIC MEDICATION

Pre-anaesthetic medication (Premedication) includes all drugs that are given prior to anaesthesia (Premedicants) so as to make the perioperative experience safer and more pleasant for the patient. For practical purposes, administration of premedication is considered as the starting lap of any surgical patient's perioperative course. Ideally, not all patients are in need of premedication, but what we see in common practice is that a fixed or a standard protocol of premedication is applied to all surgical patients. This is not to be encouraged, as the pre-anaesthetic needs of every patient differ, and administration should be done on an individualized basis[3].

BASIC PRINCIPLES OF PREMEDICATION[3]:

- a. **Alleviation of anxiety:** Anxiety is an integral psychological component of any surgical procedure. But the degree of anxiety varies from patient to patient and from procedure to procedure. Elimination or reduction of anxiety levels has been shown to have a better perioperative outcome. Drugs that are commonly employed are benzodiazepines, barbiturates and opioids.
- b. **Abolishment of memory:** No patient wants the memory of walking into the OR or being operated upon. Abolishment of short-term anterograde memory is an essential part of premedication. This is done using drugs like opioids, benzodiazepines and hyoscine. More recently, melatonin and its agonists are being tried as amnesic agents [4, 5].
- c. **Reduction of secretions:** Once anaesthetized, the patient loses his control over laryngeal reflexes, making him/her susceptible to aspiration of secretions into the pulmonary tract, leading to Mendelson's syndrome, which could prove to be fatal[6, 7]. Hence, anticholinergic drugs are commonly used for this purpose. Atropine and glycopyrrolate are the most frequently used anticholinergics, with glycopyrrolate being preferred over atropine due to its longer duration of action and its lack of central actions. In addition, anticholinergic drugs also provide vagolytic effect that is beneficial to the patient's cardiovascular status.

- d. **Pain management:** Pain management begins from the preoperative phase and continues through the operative course of the patient. Opioids via various routes are commonly used for pain management.
- e. **Reduction of acidity and volume:** It is essential to reduce the volume and acidity of gastric secretions so that damage to the epithelium can be minimized in case of aspiration or regurgitation. While prokinetic agents like metoclopramide and domperidone are used to decrease the volume of the gastric contents, proton pump inhibitors (PPIs), H₂antihistaminics and antacids are used to reduce the acidity of the contents.
- f. **Antiemesis:** Another component in the prevention of aspiration pneumonitis is antiemesis. Antiemetics agents like domperidone, metoclopramide and ondansetron are commonly employed.
- g. **Miscellaneous:** Other drugs that are given preoperatively include empirical antibiotics, tetanus toxoid and intravenous fluids.

SELECTION CRITERIA [3]:

As mentioned earlier, not all patients need all components of premedication. Selection of drugs involves various factors like ASA (American Society of Anaesthesiologists) class that ranges from class I (patients with no/minimal risk) to class V (patients with maximal risk), type of procedure, age of the patient, degree of anxiety seen in the patient, medical/surgical/anaesthetic history of the patient and the concomitant medication that the patient is on.

This requires proper and complete history taking(including history of over-the-counter drug usage and consumption of alternative medicine), a thorough clinical examination and laboratory investigations, if necessary.

ROUTES AND TIME OF PREMEDICATION[3]:

As far as possible, all premedicants are to be administered either intravenously or orally. The other commonly employed route is intramuscular. However, this is not advisable as it is painful to the patient and may add to the already-present anxiety.All intravenous premedicants are ideally to be given once the patient is shifted to the OR, whereas all oral premedicants are to be administered at least 30 to 60 minutes prior to shifting the patient to the OR.

GENERAL ANAESTHETICS:

General anaesthetics are drugs that are known to depress the central nervous system to a certain degree so as to allow the performance of surgery or other noxious/unpleasant procedures.

EVOLUTION OF GENERAL ANAESTHESIA[8] :

The earliest surgical procedures involved crude methods of anaesthesia like nerve compression, carotid occlusion, cerebral concussion, and usage of alcohol, cannabis and opium. Later came the first known and accepted modern anaesthetic agent, ether, thanks to the discovery by Dr. Crawford Long. When Dr. William Morton, a medical student, successfully staged a public demonstration of ether-based surgery, various other agents were discovered. Dr. Horace Wells, a dentist, used the gas, nitrous oxide to perform dental extraction. Dr. Edmund Andrews further popularized nitrous oxide by giving it in combination with oxygen. Dr. James Simpson, an obstetrician, conducted deliveries using chloroform. However, since chloroform is an irritant, it did not gain popularity until Queen Victoria gave birth to her seventh child under chloroform anaesthesia. Chloroform rapidly rose in popularity under the pseudonym, "Royal anaesthetic"[9]. Today, various agents that have better efficacy and safety profile have replaced these historically significant drugs.

BASIC PRINCIPLES OF GENERAL ANAESTHESIA[8]:

The three key principles of general anaesthesia are:

- a. To minimize the deleterious effects of the surgical procedure

- b. To sustain physiologic homeostasis
- c. To improve post-operative outcome

IDEAL ANAESTHETIC[8]:

An ideal general anaesthetic agent should have the following features:

- a. Reversible unconsciousness
- b. Analgesia
- c. Amnesia
- d. Muscle relaxation
- e. Autonomic reflex blunting
- f. Rapid and smooth induction
- g. Rapid reversal of effects produced
- h. Wide safety margin

Till date, there is no single ideal anaesthetic agent. The most recently discovered agent, xenon, is said to be an “almost ideal” agent but it is very expensive, hence limiting its use[10].

COMMONLY EMPLOYED AGENTS[8]:

The agents used for general anaesthesia can be divided into two broad groups, namely:

- a. **Intravenous agents**
 - i. **Fast-acting:** Thiopentone, Methohexitone, Propofol, Etomidate
 - ii. **Slow-acting:** Benzodiazepines, Ketamine, Opioids
- b. **Inhalational agents**
 - i. **Gases:** Nitrous oxide, Xenon
 - ii. **Volatile liquids:** Halothane, Enflurane, Sevoflurane, Isoflurane, Desflurane

MECHANISM OF GENERAL ANAESTHESIA[8]:

Even today, the exact mechanism of action of general anaesthesia is unknown. Initially, it was widely believed that one single mechanism of action (for example, alteration of membrane stability) was responsible for production of general anaesthesia with all agents. This was called the unitary hypothesis of general anaesthesia. However, more recently, a consensus was reached wherein it was accepted that each drug exerts its action by its own unique mechanism[3].

Even though the mechanism is still unclear, it is believed to be due to one of the two possible mechanisms – a reduction in stimulatory impulses or an increase in inhibitory impulses. As mentioned earlier, each drug acts by its own unique mechanism[11]. Table 1 shows the commonly used drugs and their mechanisms of action.

Table 1: Mechanism of action of general anaesthetics

DRUG	MECHANISM OF ACTION
Inhalational agents	Unknown
Benzodiazepines	GABA _A facilitation
Barbiturates	GABA _A facilitation
Opioids	Opioid receptor agonism
Ketamine	NMDA receptor antagonism
Propofol	Unknown

REDISTRIBUTION:

Lipophilic agents (for example, thiopentone), when given intravenously, hit the blood stream and move into the central nervous system by passing the blood brain barrier. This happens initially because the central nervous system is a highly perfused area. Once the agent exerts its effect on the nervous system, lesser-perfused areas outside the central nervous system take it up, hence ending the action of the drug. Thus, the drug is rapidly pushed out of the brain into lipid-rich areas like adipose tissue, where the drug may be stored. This phenomenon is known as redistribution[12].

MINIMAL ALVEOLAR CONCENTRATION [12]:

Minimal alveolar concentration (MAC) is an indicator of the potency of an inhalational general anaesthetic drug. MAC is defined as the least concentration of the anaesthetic agent that should be present in the alveoli to produce immobility to a noxious stimulus (usually, a surgical incision) in at least 50% of individuals. Hence, lower the MAC, more potent is the agent. Drugs like halothane and isoflurane have low MAC and are hence more potent, whereas nitrous oxide has a very high MAC making it one of the least potent anaesthetics[8].

BLOOD: GAS COEFFICIENT [12]:

Every inhalational agent has to pass through the blood stream to reach its various sites of action in the CNS, making the solubility of the agent in blood an important factor in determining its potency and rate of onset of action. If the blood solubility of an agent is low, it takes lesser concentration and hence lesser time to saturate the blood stream, making the agent much quicker and more potent. A classical example is nitrous oxide, which has very low blood solubility, making it useful in a phenomenon called "second gas effect".

SECOND GAS EFFECT [12]:

When an inhalational agent with poor blood solubility coefficient (like nitrous oxide) is given, it saturates the blood component rapidly and hence, is pushed into the CNS rapidly. Hence, there is a very high initial diffusion gradient from the alveoli to the brain. This property is made use of by giving a second drug (like halothane that normally is a slow inducer). By giving halothane along with nitrous oxide, the rate of induction is increased several fold, as nitrous oxide facilitates faster diffusion of halothane to the brain. This concept is known as second gas effect.

DIFFUSION HYPOXIA [8]:

Once the anaesthetic machine containing nitrous oxide is turned off, the negative partial pressure in the alveoli draw the nitrous oxide from the brain to the blood stream and into the alveoli. So, the respiratory tract is filled with nitrous oxide, thus decreasing the partial pressure of oxygen, leading to hypoxia. This phenomenon is called diffusion hypoxia, and is mostly seen with agents with poor blood solubility like nitrous oxide. To prevent the development of this hypoxia, it is recommended that 100% oxygen be administered just before discontinuing nitrous oxide for at least 5 to 10 minutes.

ANAESTHETIC DELIVERY SYSTEMS [13]:

The two main types of delivery systems of anaesthesia are: open drop system and machine system.

Open drop system: This is a very crude method where a mask made of multiple layers is placed over the patient's nose and mouth and the anaesthetic agent in the form of a volatile liquid is poured over it. The patient inhales the fumes produced and the anaesthetic effect is produced. This is an obsolete method in today's modern world.

Via machines: In modern practice, various types of anaesthetic machines are utilized to deliver the drugs to the patient. The types include open, semiclosed and closed. In open systems, there is no rebreathing and hence more anaesthetic agent is used per surgery. In semiclosed devices, there is partial rebreathing of the

anaesthetic agent but the carbon dioxide moiety is absorbed using soda lime or other similar chemicals. In closed devices, there is total rebreathing of both carbon dioxide and the anaesthetic agent.

RECENT ADVANCES:

Recently, there have been studies on the long-term effects of general anaesthetic agents. It has been observed that these agents on long-term may prove to be anti-ischaemic agents in the brain due to reasons unknown. So, general anaesthetics seem to exert a cytoprotective effect in the CNS. Also, there have been reports and studies on the cytotoxicity of these agents, with incidences of neurodegeneration, disturbed cognition and disturbed electrophysiology on the rise[8]. Alteration of GABA signaling is thought to be the reason for this cytotoxicity in the long run. However, further studies are required before we can arrive at a definitive conclusion.

A few experts recommend the usage of artificial tear substitutes (like methylcellulose) in the perioperative period as the patient loses the protective Bell’s phenomenon. Also, the ability to form a protective tear film layer is impaired. Reports of corneal dryness and corneal ulceration leading to blindness have come to light[14].

Also, the concept of conscious sedation is gaining popularity, especially for minor procedures and in places where there are no anaesthetic facilities. Conscious sedation is the procedure in which the consciousness level is depressed but the patient retains the ability to maintain a patent airway. Also, the patient is able to respond to verbal commands. Benzodiazepines and opioids are commonly used, as there are specific antagonists available for these agents in case of toxicity. Propofol and nitrous oxide are also being tried for the same[15, 16].

LOCAL ANAESTHETICS:

Drugs that act on nerve fibres and cause reversible loss of action potential generation and transmission, hence resulting in loss of sensory (and rarely, motor) function, are known as local anaesthetics [8].

EVOLUTION OF LOCAL ANAESTHESIA[17]:

The earliest documented use of local anaesthesia was the use of Coca leaves (from which cocaine is derived). Dr. Carl Koller in the late 19th century is credited with the first procedure done under local anaesthesia. This was followed by other agents like benzocaine, procaine and tetracaine when finally in 1948, the “surgeon’s ally”, lignocaine was introduced.

MECHANISM OF LOCAL ANAESTHESIA [18, 19]:

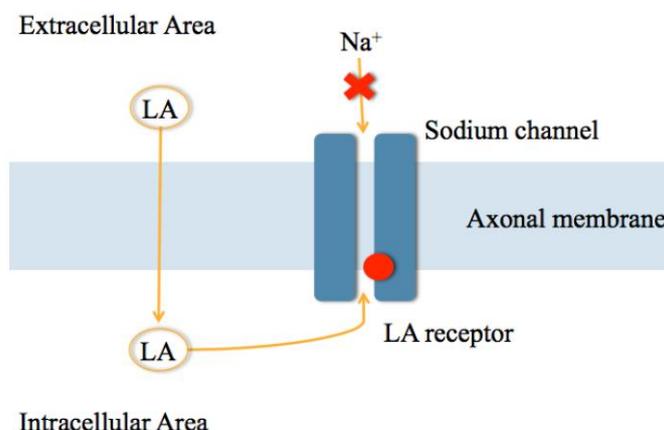


Figure 1: Mechanism of action of local anaesthetics

Local anaesthetics are molecules that have a hydrophilic moiety on one end and a lipophilic moiety on the other end with a connecting ester or amide group in between. They use the lipophilic side to cross the axonal membrane and get into the intracellular domain. The receptor for local anaesthetic action is located on the intracellular face of the sodium channels, as shown in figure 1. Once the local anaesthetic binds to the receptor on the sodium channels, there is prolonged inactivation of the channel due to prevention of sodium entry into the cell. Hence, there is no generation of new action potential. Also, the already-generated action potentials are not spread further.

Three different coatings, namely epineurium, perineurium and endoneurium, line every nerve fibre. The local anaesthetic has to pass through these lining membranes to come in contact with the nerve fibre. Further, the outer concentric circle of nerve fibres supplies the more proximal areas while the inner fibres supply the distal areas. Hence, the proximal areas are anaesthetized ahead of the distal ones. Autonomic fibres are more sensitive as opposed to somatic fibres. Among the various sensory modalities, pain is abolished first, followed by temperature, touch and deep pressure.

COMMONLY EMPLOYED AGENTS [18, 19]:

The commonly used local anaesthetics can be grouped under two types, based on the bonding chain that connects the hydrophilic and the lipophilic moieties.

- a. **Ester-linked agents:** Cocaine, Procaine, Benzocaine, Chlorprocaine
- b. **Amide-linked agents:** Lignocaine, Prilocaine, Bupivacaine, Dibucaine

Between the two groups, the amide-linked agents are preferred because they are:

- a. More potent
- b. Longer-acting
- c. Less liable to cause hypersensitivity reactions
- d. Not hydrolyzed by plasma esterases

ADDED VASOCONSTRICTORS[18, 19]:

The concept of adding a vasoconstrictor to a local anaesthetic agent has been in practice for ages. The combination has its own set of merits and demerits, with the merits outweighing the demerits. Common agents used as vasoconstrictors are adrenaline (in the concentration of 1:50,000 to 1:200,000) and felypressin (a vasopressin analogue).

The merits of using such combinations include:

- a. Prolonged action of the anaesthetic
- b. Enhanced intensity of the block
- c. Reduced systemic toxicity of the anaesthetic
- d. Blood-free field for surgery
- e. Lesser amount of anaesthetic required

The demerits include:

- a. Delay in wound healing
- b. Risk of hypertension
- c. Risk of arrhythmias

LOCAL ANAESTHETIC IN INFECTED TISSUE [20]:

The usage of local anaesthesia usually results in therapeutic failure, manifesting as no/poor loss of pain. The causes may be:

- a. Lower pH in infected tissue leading to ionization of the local anaesthetics (weak bases), leading to poor penetration across the membrane
- b. Increased blood flow to and away from the infected region, leading to washing away of the anaesthetics from the site of action
- c. Interference by the various inflammatory mediators

EMLA [19, 20]:

EMLA (Eutectic Mixture of Local Anaesthetics) is a combination of two anaesthetic agents (lignocaine and prilocaine in equal proportions, either 2.5% each or 7% each) wherein their melting point is lowered to 25°C rendering the combination more lipophilic, hence giving it the ability to penetrate intact skin after surface application. Anaesthesia is achieved up to a depth of 5mm for a duration of 1 to 2 hours. EMLA is applied 30 to 60 minutes prior to the desired procedure (commonly, intravenous cannulation, venesection).

TECHNIQUES OF LOCAL ANAESTHESIA [18, 19, 20]:

- a. **Surface anaesthesia:** Local anaesthetics are usually unable to penetrate intact skin (EMLA being an exception). Hence, surface anaesthesia excludes the usage on intact skin and correlates more with the usage on abraded skin and mucous membranes. Various formulations used include gels, ointments, sprays, patches, etc.
- b. **Infiltration anaesthesia:** This technique involves subcutaneous instillation of the anaesthetic agents around the desired site of action. It is commonly used for minor incision and excision procedures. Usually, the volume of drug used will be disproportionately higher as compared to the effect produced. Further, multiple needle pricks are required to instill the drug all around the desired area, making it an uncomfortable technique for the patient.
- c. **Conduction block anaesthesia:** The technique involves injected the agent in/around a major nerve root (field block) or a nerve trunk (nerve block). Lesser volume is required as compared to infiltration technique. Also, the duration of action is longer.
- d. **Intravenous regional anaesthesia (Bier’s block):** Bier’s block is used for isolated procedures involving either the upper or the lower limb. A tourniquet is tied tightly around the arm or the upper thigh, following which the drug is injected intravenously. This makes the local anaesthetic action restricted to the limb, by preventing venous return. However, cardiotoxic drugs like bupivacaine are not to be used.
- e. **Spinal regional anaesthesia:** Here, the local anaesthetic is injected in the subarachnoid space between L3-L4 or L2-L3 spaces. It is used for surgeries below the level of the umbilicus, commonly in inguinal or obstetric procedures. Complications include PDPH (Post-Dural Puncture Headache) due to leakage of CSF, which can be prevented by using a small-bored needle or by preloading the patient with fluids. This procedure is technically easier as compared to epidural anaesthesia.

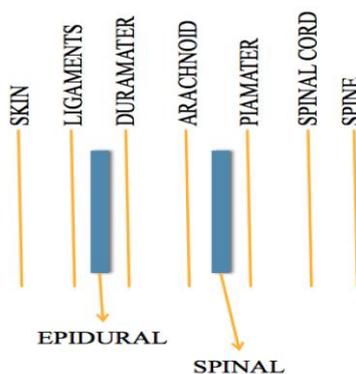


Figure 2: Injection sites for epidural and spinal anaesthesia

- f. **Epidural regional anaesthesia:** The drug is injected in the epidural space. Usually, a catheter is placed in the space so as to give further doses as and when required. This technique requires expertise.

LIPID RESUSCITATION[21, 22]:

When a local anaesthetic like bupivacaine is given intravenously either as part of a regimen or inadvertently, the resultant cardiotoxicity is inevitable. Lipid resuscitation is a rescue therapy in which lipids are pushed intravenously, forming a lipid reservoir that will attract the lipophilic local anaesthetic molecules and excrete them via renal elimination, thus reducing the cardiotoxicity likely to be seen in the patient. This is a controversial technique as injection of lipids into the blood stream, by itself, can lead to morbidity and mortality in the form of fat thrombosis and embolism. However, this is considered as a radical treatment option for such cases, and further efforts to increase the safety of this technique are under development.

NEUROMUSCULAR BLOCKERS:

Neuromuscular blockers are drugs that act on the neuromuscular junction (NMJ) and produce skeletal muscle relaxation with or without paralysis.

EVOLUTION OF NEUROMUSCULAR BLOCKERS[23]:

The use of neuromuscular blockers probably started with “curare”, the popular arrow poison in South America. It was used to paralyze animals when hunting for food. Later on came the modern synthetic agents, d-tubocurarine and decamethonium.

COMMONLY EMPLOYED AGENTS[23]:

Neuromuscular blocking agents can be broadly divided into two groups, namely depolarizing (non-competitive) blockers like succinylcholine, and non-depolarizing (competitive) blockers like d-tubocurarine, atracurium, pancuronium, etc., based on their mechanism of action. They may also be grouped on the basis of their chemical structure into acetylcholine-like compounds (succinylcholine), steroidal compounds (like pancuronium, rocuronium) and benzylisoquinoliniums (like atracurium, d-tubocurarine). Further, they can also be subdivided based on their onset/duration of action, into ultrashort, intermediate and long acting agents.

MECHANISM OF NON-DEPOLARIZING BLOCKADE[23, 24]:

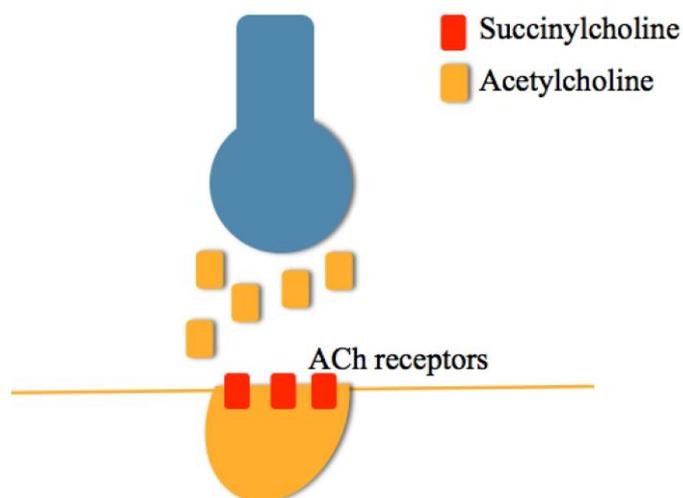


Figure 3: Mechanism of action of non-depolarizing blockers

The non-depolarizing (competitive) blocking drugs act by competing for the acetylcholine (ACh) receptors, hence preventing the binding of ACh to its nicotinic receptors (N_M) leading to loss of depolarization,

and hence passive skeletal muscle relaxation, as depicted in figure 3. This inhibition is slow to develop, and surmountable at higher doses of ACh.

MECHANISM OF DEPOLARIZING BLOCKADE[23, 24]:

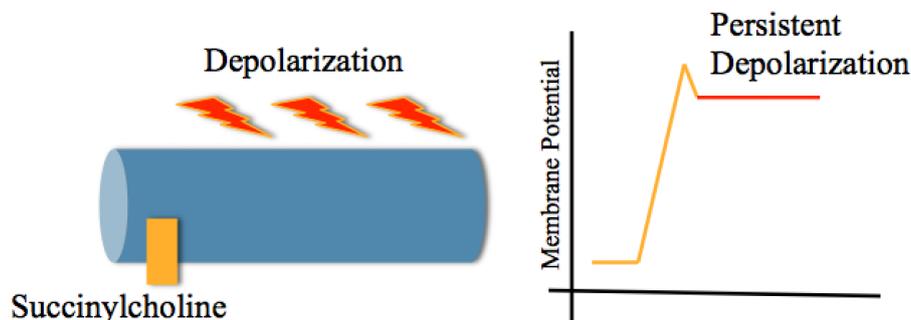


Figure 4: Mechanism of action of depolarizing blockers

Succinylcholine, a depolarizing blocker, is similar to ACh in its chemical orientation, hence resulting in binding of succinylcholine in the place of acetylcholine, causing a depolarization synonymous with that produced by ACh. However, acetylcholinesterases degrade ACh but succinylcholine has to be metabolized by pseudocholinesterases. Therefore, the concentration of succinylcholine is constant in the NMJ, leading to a state of prolonged depolarization, as shown in figure 4. This causes initial twitches and tremors (that may later translate to postoperative muscle pain and weakness). Since there is no repolarization, further action potentials cannot be generated, and hence, there is muscle relaxation.

MONITORING OF NEUROMUSCULAR BLOCKADE[25, 26]:

Other than direct visual / subjective monitoring, there are electrical stimulatory methods that are used to monitor the extent and degree of neuromuscular blockade in the patient. This objective testing requires the involvement of peripheral nerves and muscles. The most commonly selected (gold standard technique) nerve-muscle combination is the ulnar nerve-adductor pollicis duo. The various electrical stimuli that are used in clinical testing are as follows.

- a. **Single twitch:** A single submaximal electrical stimulus is given, and the response is checked. Since there is only one response (no control), this method is the simplest and the least sensitive of all.
- b. **Double burst:** Here, two electrical stimuli are given with adequate time duration in between, for proper recovery.
- c. **Train of four:** This is the most commonly used technique for monitoring, wherein four rapidly successive stimuli are given. The heights of responses (T_1 to T_4) are measured. The ratio of T_4 to T_1 gives the Train of Four ratio (TOFR). Normal TOFR is said to be around 1. Adequate block is said to be achieved if the ratio is less than 0.5 to 0.6 (in case of competitive blockade). The phenomenon of slowly reducing responses, in a competitive blockade, is called "Fade phenomenon". In case of a non-competitive blockade, all four responses are equally reduced, hence maintaining the TOFR at 1 (as shown in figure 5).

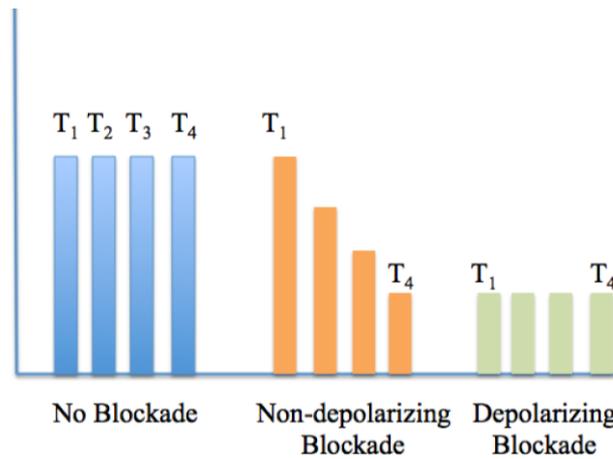


Figure 5: Train of Four responses

- d. **Tetanic count:** In this technique, a maximal or supramaximal stimulus is given so as to induce tetany of the muscle fibres.
- e. **Post-tetanic count:** This method is commonly used in combination with “tetanic count”. Since there would have been a storage pool of ACh following a tetany, the response immediately following tetany is normally bigger than the tetanic response. In case of competitive blockade, the response is decreased.

SUGAMMADEX[27, 28, 29]:

Any neuromuscular blocker (with the exception of ultrashort-acting drugs) needs a reversal agent that can normalize the existing muscle relaxation and weakness. Other than the routinely-used anticholinesterases, a novel agent called Sugammadex has been introduced (mainly for reversal of neuromuscular blockade by pancuronium, vecuronium and rocuronium). Sugammadex is a gamma-cyclodextrin that chelates the neuromuscular blocker and excretes it via the renal elimination pathway. It is said to have a very rapid reversal onset of less than 5 to 7 minutes, making it a highly effective reversal agent.

MANAGING CHRONIC MEDICATION:

It is estimated that almost 44% of surgical candidates are on one or more chronic medication. Theoretically, all drugs can be given up to 2 hours prior to the procedure. And ideally, all drugs have to be continued without a break due to various reasons like worsening of disease, onset of withdrawal reactions and destabilization of the patient’s homeostatic systems. Commonly, drugs that increase the risk of surgical or anaesthetic complications and drugs liable to cause interactions with anaesthetic agents are to be stopped. But, there is no fixed or general rule to stop or continue chronic therapy. Intervention of chronic medication has to be individualized on a patient-to-patient basis.

The complete drug history has to be elicited, including any over-the-counter drug intake and herbal medicines, if any. Past history of drug interactions with anaesthetic or pre-anaesthetic drugs has to be obtained as well.

DRUGS TO BE STOPPED PREOPERATIVELY[30, 31]:

- a. **Cardiovascular drugs:**

Diuretics are preferably stopped in the perioperative period for two reasons – increased risk of hypovolaemia, and discomfort to the operated patient in the form of frequent urination or risk of urinary infections in a catheterized patient.

There is insufficient evidence to stop angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Hence, a decision has to be made, weighing the risks and benefits of stopping the therapy.

Hypolipidaemic drugs (except statins) are preferably stopped, owing to drug interactions and risk of myopathy. Statins are not stopped as the available evidence suggests increased cardiovascular morbidity in the perioperative period on stopping them[32].

b. Central nervous system drugs:

Lithium is recommended to be stopped at least 1 day prior to the procedure, owing to its drug-drug interactions and sodium-like action in the kidney[33].

Irreversible monoamine oxidase inhibitors (MAOIs) are to be stopped at least 14 days before any procedure, and replaced by reversible MAOIs[33]. Irreversible MAOIs are more prone to cause serotonin syndrome and cheese reaction.

Evidence is lacking with the cessation of tricyclic antidepressant (TCA) therapy. A few practitioners prefer to stop TCA therapy 2 to 3 days preoperatively[33].

c. Endocrine medication:

Oral contraceptive pills (OCPs), especially those with an oestrogen component in them, are to be interrupted at least 4 weeks preoperatively, as they pose the risk of thrombosis and embolism perioperatively. After the procedure is done and the patient has recovered, the OCPs are restarted from a new menstrual cycle[34].

Corticosteroid therapy is not to be stopped for any reason, as surgery is a stressful condition and stopping therapy may lead to hypothalamo-pituitary-adrenal (HPA) axis suppression. On the contrary, the dose of steroids is to be increased or maintained, depending on the regimen that the patient is on. If the patient is on steroids for less than 30 days or on an alternate day regimen, the same dose may be continued. If the patient is on high dose steroid therapy for more than 30 days, then the dose has to be further increased, or an intravenous dose of 100mg (Hydrocortisone) is given before surgery. If the patient is on low dose steroid for more than 3 weeks, the decision to continue the same dose or to increase the dose rests on the clinician's judgment[35].

d. Haematologic medication[36]:

Low dose aspirin (used as an antiplatelet) has to be stopped at least 4 days preoperatively (ideally, 7 to 10 days prior to the procedure) as bleeding risk is raised several fold. As aspirin acetylates the cyclo-oxygenase (COX) in the platelets irreversibly, the platelet function is lost permanently till fresh platelets are synthesized. Hence, the duration of treatment interruption correlates with the life span of platelets (7 to 10 days). However, for patients with high risk of thrombosis and embolism, aspirin therapy is continued as risk of stopping outweighs the benefit.

Warfarin acts by inhibiting the production of vitamin K-dependent clotting factors (II, VII, IX, X) and has to be stopped 4 to 5 days preoperatively.

Low molecular weight heparin (LMWH) can be stopped just 12 to 24 hours before the procedure.

In case of stopping anticoagulant therapy with conventional heparin and warfarin in high-risk (of developing thrombosis) patients, bridging therapy with LMWH can be initiated in the early preoperative period.

e. Miscellaneous drugs[37]:

Other drugs that need to be stopped are theophylline (drug-drug interactions are plenty) and non-aspirin NSAIDs (Non-steroidal anti-inflammatory drugs) as they may have antiplatelet action of their own.

DRUGS TO BE CONTINUED PREOPERATIVELY[38]:

Most of the other drug groups including beta blockers, calcium channel blockers, antiepileptics, antiarrhythmics, digoxin, antipsychotics, proton pump inhibitors, statins and antidiabetic agents are to be continued without a break. This is a general concept based on the risk-benefit analysis of stopping the therapy. However, as mentioned earlier, management of chronic medication has to be individualized based on the patient's requirements.

DRUGS WITH MODIFICATION OF ROUTE:

Change of route is normally advised when the patient is unable to take his oral medication, and when the medication is essential to maintain homeostasis of the patient's internal environment. The most common drug group with change of route is the antidiabetic group. The patient is shifted from oral hypoglycaemic agents (OHAs) to parenteral insulin for better diabetic control and better monitoring[38]. Also, inhaled corticosteroids and beta agonists are changed over to parenteral bronchodilator therapy.

CONCLUSION

Perioperative mortality is said to be preventable in nearly 50% cases. Proper understanding of the basic concepts involved in the preoperative management of any patient forms the basis of decreasing these high mortality and morbidity rates. Further, extensive research is being performed to arrive at the exact mechanism of general anaesthesia and to generate more target-specific agents with lesser adverse effects. The future looks bright, with the amount of research under way in this domain.

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