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A Review of Anaesthesia Drug (Propofol and Remifentanil)

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Abstract

It sole responsibility of anesthetized to have knowledge about the physical and chemical characteristics of every drugs and its role. At foremost the cautious standard of drug delivery technique with continual intravenous procedure isvery importance to avoid inadequate dosage level to the patient. Development of the new prototype based regulated method are able to say about dosage level given to the patient, but they are truly depends upon the patient body nature. So it must have an adequate awareness about characteristic of each drug before it is used to the humanbody. At finally we had review and examine the outcome of collective effect of commonly used two drugs Propofol (hypnotic) and Remifentanil (opioid) and its lustiness and reliability during operation.

Keywords : Anesthetized, Intravenous, Propofol, Remifentanil, hypnotic, opioid

I. Introduction

A drug is a substance (with the malformation of food and water) when consumeby the human body, which alter the psychology behavior of human being either physically and /or interpersonally. Daily usage drugs are such as (eg. Alcohol, caffeine and tobacco) or banned type such as (eg. Cannabis, ecstasy, cocaine and heroin) [30]. Mainly drugs are categorized into four main classifications they are

- Stimulants (eg. Cocaine)
- Depressants (eg. Alcohol)
- Opium-related pain killer (eg. Heroin)
- Hallucinogens (eg. LSD)

A drug may be called as an Anesthetic (American English) or Anaesthetic (British English) used to persuade anesthesia – the alternate word, it is a transitory loss of outrage or consciousness.

II. Definition of Anaesthesia

Anesthesia[ăn′ĭs-thē′zhə] is a complete or partial loss of motion to nudge or pain, caused by a nerve fiber wound or disorder or induce purposely, specifically managing the anesthetic drugs, to give healing therapy. The basic categorizations of Anesthesia are shown in the Fig.1.

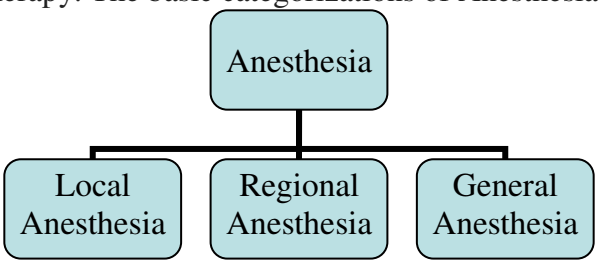

Fig.1. Classification of Anesthesia

- Local Anesthesia: Immobilize a specific location of the human region. The sufferer will be at awake state.
- Regional Anesthesia : It obstruct the pain in an exact location of the human region., eg: arm or leg
- General Anesthesia: It makes the whole body as immobilize state and make the sufferer in insensible state.

III. Stages of Anaesthesia

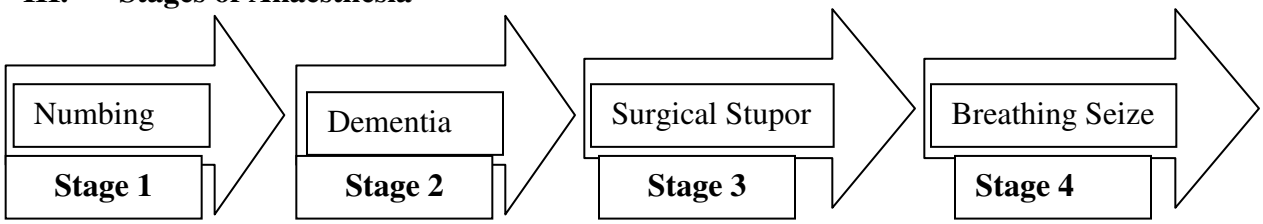

Fig.2.Stages of Anesthesia

The dosages of anesthesia drug are shown in the Fig.2 they are 4 stages, above the fourth stage which may leads the patient to the coma stage [3]. So the main aim to regulate the general anesthesia is too given by a stage of mutable unconsciousness with sufficient analgesia and muscle loosening for operation procedure in such a way that it does not harm the patient's health. The knowledge of safe anesthesia requires, practical talent and sharp consciousness of the patient's condition at all times.

IV. History of Anaesthesia drug

In ancient times the people uses different types of nature based drug such as (opium poppy, Coca leaves, Alcohol, Phlebotomy) for a surgical operation

John Snow (1813 – 1858): Is the father of anaesthesia who had made anaesthesia as a technical term by showing how the patient body accept it and accordingly respond to it. Later on the year 1846 the word Anaesthesia is initiated by Oliver Wendell Holmes. Further it is developed and first successful surgical anesthesia (sulfuric ether) given to the patient and it succefully completed by Mr.William Morton (1819 – 1868) [5]. In the modern era of Anesthesia is developed in 19th century by "Association of Anesthetists of Great Britain and Ireland" formed (1932) founded many types of drugs are shown in the Fig.3 and introduced in surgical operation such as.

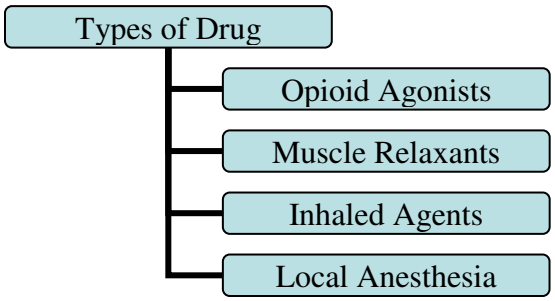

Fig.3. Types of Drugs

There are many drugs are introduced till now most frequently used drugs are (Propofol, Etomidate, Barbiturates similar to methohexital and thiopentone/ thiopental, Remifentanil, Benzodiazepines such as midazolam). From that two major drugs are Propofol and Remifentanil we are going to analyze detail about two drugs in this paper.

V. Propofol

It is an inoculation method of drug used in the patient. Propofol otherwise called as DIPRIVAN®. It is chemically chronicle as 2, 6-diisopropylphenol [11]. It is imitative of phenolic anatomy shown in the below Fig.4 compose of oil-in-water mixture. The drug was introduced in the year 1984 and further developed by many young scholastic anesthetists. Finally it has been introduced by Paul F.White in sedation of instinctively ventilated adults in ICU (1993) [26].

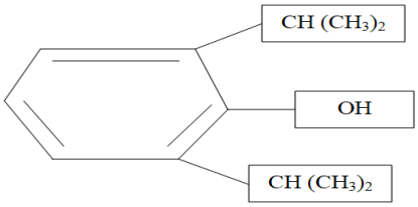

Fig.4. Structure of Propofol

It has relaxing and drowsiness properties [5]. Propofol is marginally resolvable in water and made up of white, oil-in-water mixture. The pKa is 11. The octanol/water separation constant for Propofol is 6761:1. It consist of other mixture are Soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL); and disodium edetate (0.005%); with sodium hydroxide to regulate pH [28].

a. Physical Properties

The basic physical properties of Propofol are given in Table.1 shown below.

Table.1. Physical Properties of Propofol

Molecular Formula	$C_{12}H_{18}O$
Molecular Weight	178.27g/mol
pH	6 to 8.5
Density	$0.9 \pm 0.1 g/cm^3$
Boiling Point	256 ± 0.0º c at 760 mmHg
Vapour Pressure	0.0 ± 0.5 mm Hg at 25ºC
Enthalpy of Vaporization	51.3 ± 3.0kJ / mol
Volume of distribution	60 L/ kg (for Healthy Person)

b. Pharmacodynamic Properties

Propofol is narcotic-somniferous drugs which are used during the operation to keep the patient in tranquilizing stage. Constant dosages of Propofol (Diprivan®) intensify the sedation in a drug dosage-dependent manner. The objective of plasma propofol dosage level given to the patient is determined to attain a Ramsay sedation score of 2-5 ranged from 0.25 to 2.0mg/L [11]. The disclosure from propofol sedation is depends upon on the some of the factors are duration

and size of the patient, depth of narcotic given. Propofol object is a dose-dependent which reduces the blood pressure and heart rate. Intramuscular injections of a remedial dose of propofol make hypnosis quickly with minimum stimulation, normally within the 40 sec from the starting stage of infusion.

c. Pharmacokinetic Properties

Propofol is mostly Oily organic compounds expedite speedy diffusion to the blood-brain blockade and a quick start of the deed [5]. The pharmacokinetic effects arespecifying by 3 compartmental designs:

- Rapid start diffusion from blood into tissues
- Fast reallocation and metabolism separation.
- Slow return from insertion tissues into the arteries

Propofol has a rectilinear pharmacokinetic portrayal. At stable level, the acceptance of propofol is depends upon the biological system and diffusion to peripheral epithelium [4]. It is comprehensively metabolized and discharged in urine (≥88%), mostly as inert metabolites [11]. Different type's aspect like age, sex, weight and already known diseases may be change the pharmacokinetic characteristic of propofol

Female: It represents the high amount of diffusion rate.

Elderly: It reduces the clearance rate and reduces the central compartment volume.

Children: It represents the increase in middle compartment volume and quick concurrence.

d. Admissibility

Propofol has a cardiorespiratory sedative result, which can lead the way to low blood pressure and decrease the pulse rate. In specific, tablet dosages of propofol are related with noticeably momentary low blood pressure. Specific care should be taken while giving propofol dosage to the elderly patient who are physically unsteady or blood disorder. Discomfort on inoculation is usual with propofol when they are managing into external veins [20], but it can be decreased by using the wide range of veins in the lower arm. Hypertriglyceridemia is related with propofol dosage of > 3 days [11]. In Fig 5 shows the response of propofol in the blood level by EEG score

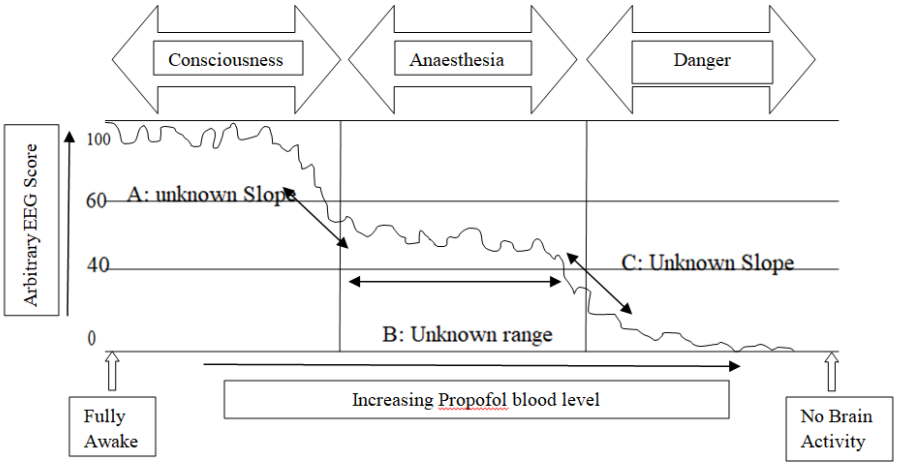

Fig.5. Blood level of Propofol

e. Mechanism of Action

The efforts of Propofol concern a positive attenuation of the self-consciousness purpose of the neurotransmitter gama-aminobutyric acid (GABA) through GABA-A receptors. It reduces the amount of isolation of GABA from its sense-organ, thereby extending the time duration of the GABA operated by opening of chloride channel which result action potential of plasma membrane. The flow processes of GABA receptors are shown below in the Fig.6.

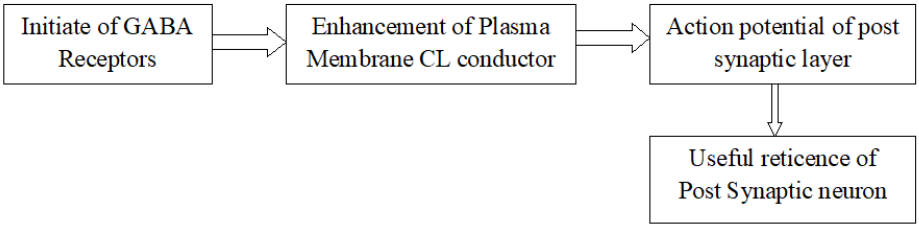

Fig.6. Flow Process of GABA

The Fig.7 is shown below describes the fall of body fluid propofol levels following injection at different time interval to the patient in ICU ward.

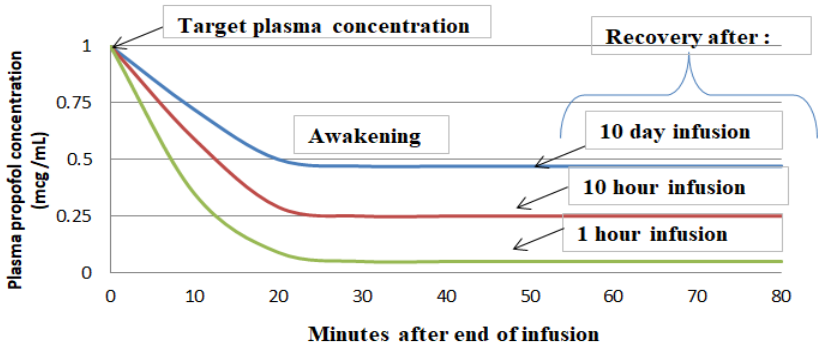

Fig.7. Plasma Concentration of Propofol

f. Significance and utilization

Initialization and continues observance of stupor care in elderly an only combines of restfulness and epidural anesthesia of patient depend upon the age factor. They are extubation, manually oxygenated patient by propofol at which can be used without any related drug for sedative.

g. Excessive dosage of drug:

There is no antitoxin of Propofol. If excessive dosage occurs in propofol level it should be stopped at instant. Over dosage may cause the cardiovascular respiratory recession. It should be cure by manual oxygen ventilation. It also requires by lifting up the patient's legs, and raising the arterial liquid rate of flow. It also needs to control persuade liaison and antimuscarinic drug. The Table.2 shows the basic characteristics of propofol.

Table.2. Characterstics of Propofol

Characteristics	Alkyl phenol is arterial narcotic source. It is used in general anesthesia. It also maintains the dosage level in each case by continuous inoculation.
Classification	Induction Agents
Dose	Induction**:** 2-2.5 mg/kg arterial for elders Induction: 0.125- 0.3 mg/kg arterial for infant Sustentation of numbness:100-200 µg/kg/minute Drowsiness: 40-100 µg/kg/minute
Time span	Around 5-8min after one time dosage level. Equilibrize effect is more in continuous infusion.
Rejection time	Abrupt change from central nervous system (CNS) into lean body section for instantaneous wake up.
Drug Effects	Central Nervous system, Chorionic villus Sampling, Respiratory
Contraindications	Soy allergy
Advantage	Rapid onset, Rapid recovery very widely used
Disadvantages	Can cause respiratory dejection and slow heartbeat.

h. Future intuition.

Additional assessment is also required to obtain the knowledge of interaction procedure and risk factor of Propofol related to injection symptoms. Usage of Propofol injection in younger patients has been scrutinize because for long time propofol dosage level of 6% when it has been used < 4mg/kg/ hr dosage level can be changed in future execution.

VI. Remifentanil.

Remifentanil basically come under the fentanyl group of semisynthetic anodyne which are supplement to anaesthesia. It is precise mu-type-sedative sense-organ protagonist which reduces the peripheral nervous system tone, and seed hypoventilation and pain-relieving. Initially it, has been accept bythe United States Food and Drug Administration in 1996[1] and patented by Glaxo Wellcome Inc [9]. It is a stupor pain reliever used during the operation. The visceral motor systems give rise to the trouble-free of post-operative and anesthetic period. It is a dominant in ultra-short acting semisynthetic anodyne drug. It is used for narcotic as well as together with other antibiotic for use in general anesthesia. Generally remifentanil are combined with propofol for increase the dose of narcotic and low dose of drowsy state due to the interactive between two drugs. A brand name is Ultiva (remifentanil hydrochloride). The basic chemical structures of remifentanil are shown below in the Fig.8.

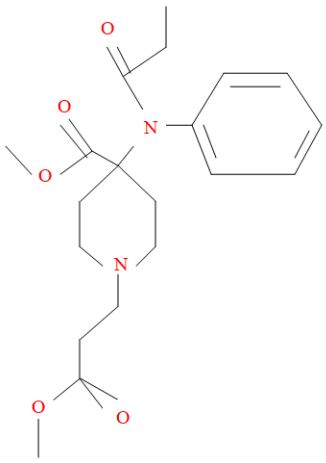

Fig.8. Structure of Remifentanil

Remifentanil free base cocaine is put together with glycine. It is prime proscriptive neurotransmitter in the cerebrospinal nervous system of marsupial [5]. Remifentanil is obtained as a white powder which can easily liquefy in water, typical saline solution. But it is not steady in mixture state for long time, it must be changed within 24hours initial to use.

a. Physical Properties

The basic physical properties of Remifentanil are given in Table.3 shown below.

Table.3. Physical Properties of Remifentanil

Molecular Formula	$C_{20}H_{28}N_2O_5$
Molecular Weight	376.447 g/mol
pH	3
Density	$1.2 \pm 0.1 g/cm^3$
Boiling Point	487.8ºC at 760 mmHg
Vapour Pressure	$1.22*10^{-8}$ mm Hg at 25ºC
Enthalpy of Vaporization	75.4 ± 3.0kJ / mol
Volume of distribution	350 mL/kg 452±144 mL/kg (infant) 223±30.6 mL/kg (adults)

b. Pharmacodynamic Properties

Remifentanil is a clear μ effector protagonist whose sedative sensory-receptor pursuit has been explained in vitro. The drug characteristic of remifentanil is provoked by anodyne such as naloxone. The outcome of remifentanil is on the peripheral nervous system are mirror on the Electroencephalograph (EEG). By giving excessive dosage of remifentanil the process are decelerate the frequency and a rise in magnitude that changes reduces the spectral edge value[7].These transpose are depends as the EEG impression on this drug. The breathing

dejection is nearly to the remifentanil blood accumulation and it has been utilized to calculate the drug effect for pharmacodynamics casting design [13]. It is dependent upon on the dosage level it reduces in pulse rate; venous blood pressure and rate of flow [14].The undesirable effect incorporate retching, vomiting and muscle stiffness [7]. During surgery the consciousness has been associated with remifentanil drug level [17].

c. Pharmacokinetic Properties

Remifentanil is a poor base with a Pka of 7.07. In tag of the swiftness which congregation level reduces when injection dosage is terminated, remifentnil is extremely unlike from the further fentanyl congeneric. The chemical features accomplishing tremendously protein enclose stimulant, more or less 70% in which 2/3rd of binds to alpha-1-acid glycoprotein.

The importance of human total mass on remifentanil pharmacokinetic property is analyzed. This specifies that overweight sufferer should not gain a weight relative rise in amount of the drug given, by giving it may lead to crucial symptom such as hypotension and dysrhythmias. The spell needed to attain a body fluid at a constant rate of remifentanil by beginning an uninterrupted injection with any need of authority of doses in an around 15min [3]. In transgenesis studies with atracurium, mivaurium, esmolol, echothiophate and midazolam revealed no reluctance of remifentanil hydrolysis in total human blood by this type of drugs.

d. Dosage and Controlling

Remifentanil drug is controlled by in person particularly qualified in anesthetic. They must be well known about the maintenance and patient breathing flow rate. At constant insertion of remifentanil must be controlled by either attune injection gadget into impetuous IV line or via anexclusive IV line. The injection line should be joined to the tracheostomy cannula, to reduce the possible dead spot. It is firm for one day when it's kept below at 25ºC after rearrangement and additionally concentration one of the below methods.

- Fumigate water for inoculation.
- 5% Dextrose inoculation.
- 5% Dextrose and 0.9% sodium infusion.
- 0.9% sodium chloride infusion.
- 0.45% sodium chloride infusion.

e. Admissibility

Remifentanil drug is very well tolerated in ICU room with a mechanical external respiration. The frequently occurring negative impact of remifentanil receiver associate with to its μ-drugs protagonist characteristics. It is similar to the fentanyl or morphine used in ICU ward with a momentary mechanical external respiration for upto 3 days. There was no remarkable variation between remifentanil and fentanyl receiver in the occurrence of sickness, temperature or hyperpyrexia [5]. The generally side effects occur during remifentanil dosage is cardiac arrhythmia and vomiting. It is well suitable for pediatrics patient. In Fig.9 shows the peak time effect of Remifentanil with other type of drugs.

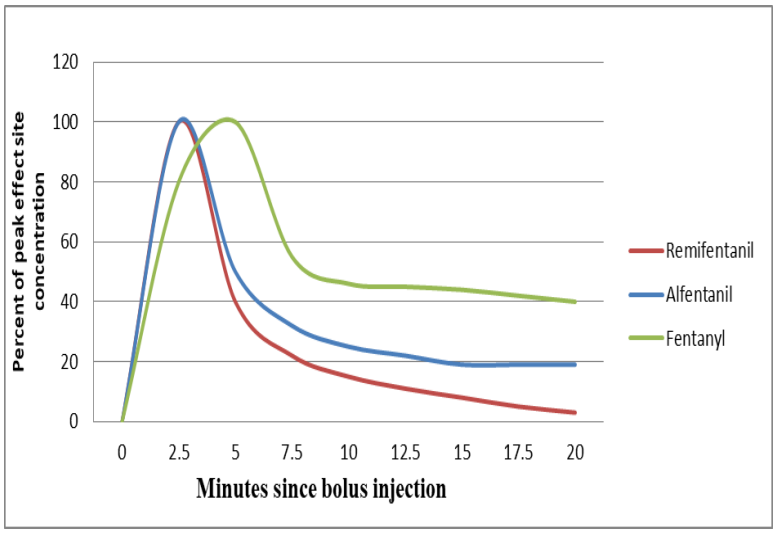

Fig.9. Comparison of Peak Effect Times of Remifentanil

f. Mechanism of Action

Remifentanil is a powerfull, artificial (man-made) drug that is replica of fentanyl. A 0.1mg dosage of remifentanil is almost equal to 10mg of fentanyl regulated by intravenous syringe. It triggers sensory organ nerves in the brain to raise the threshold to discomfort and diminish it. It also available in the form of transcutaneous and intramuscular form. Depth of Anaesthesia of Remifentanil drug in TIVA and TCI method are shown in below Fig.10.

Remifentanil (Ultiva)

TIVA – dosage	**Anesthesia Depth**	**TCI-dosage**
µg/ kg/ min		ng/ml
0.05	Drowsiness / Awake state	1.3
0.10	Surgery	2.0
0.20	Anesthesia during surgery	3.0
0.25	Suctioning	6.0
0.35	Strong pain stimulant	7.5
0.50	Deep Anesthesia	10.0 12.0
0.80	Very Deep Anesthesia	15.0
Infusion Dose		**Target Concentration**

Fig.10. DOA of Remifentanil

g. Excess Dosage level

In the happening of excess dosage:

- Desist managing
- Continue watching the patient breathing
- It should be supervised with pure oxygen.
- Important is to have a sufficient knowledge about cardiovascular working.

If miserable in breathing occurs with muscle inflexibility, neuromuscular blocking drug is vital to assist or controlled breathing. IV fluid and blood pressure are the for the therapy of hypotension and other type of sensitive measures are needed. The time span of breathing dysthymia followed by excess dosage is unexpected to the excess duration of the remifentanil drug induced to the patient. Excess dosage indication are an add on to the pharmaceutical inevitable measures of remifentanil. In Table.4 shows the basic characteristic of Remifentanil.

Table.4. Characteristic of Remifentanil

Characteristics	Artificial opioid analgesic (ultra short-acting); Supplement to the anesthesia.
Classification	Opioid agonists and antagonists
Dosage level	Induction: 0.3-1 µg/kg Sustentation of numbness: 0.1-1 µg/kg/ minute (by injection) Drowsiness: injection rate 0.05 – 0.1 µg/kg/minute
Time span	5-10 minutes; conditions sympathetic half time 3 minutes
Rejection time	Indiscriminate blood-tissue esterase's (small-organ unconstrained)
Drug Effects	Central Nervous system, Chorionic villus Sampling, Respiratory, Gastrointestinal
Advantage	Short-lasting of action, It can be back-pedal with naloxone drug
Disadvantages	Nausea / vomiting, Chest wall rigidity

VII. Interaction between Propofol and Remifentanil

During surgery patient accept sleep-inducing drug (eg. Propofol) to make sure to attain unconsciousness state. In furthermore the patient accepts an opioid dosage drug (eg. Remifentanil) to reduce the pain. In some of the cases the usage of Remifentanil drug is increased comparing with the mixture of Propofol. In the current usage of anesthesia are stated below.

i) In ultra-modern drug delivery systems similar as TCI [8] it permit for an exact mixture and cautious controlling in patients with restricted treatment index;

ii) In some of the cases, Remifentanils use as single drug for painfull surgery in patients breathing spontaneously.

iii) Concurrently, Remifentanil has allowed has key in technical based research, which leads to the better understanding of rehabilitation of patient.

There are different types of models are used between injecting narcotics and painkiller have been explained [3]. Pharmacodynamic (PD) characteristics describe the interaction between two drugs concentration with their incorporate surgical drug reaction shown in exterior prototype.

The rate at which both remifentanil and propofol drug given to the patient during the operation are shown in the below Fig.11 detail.

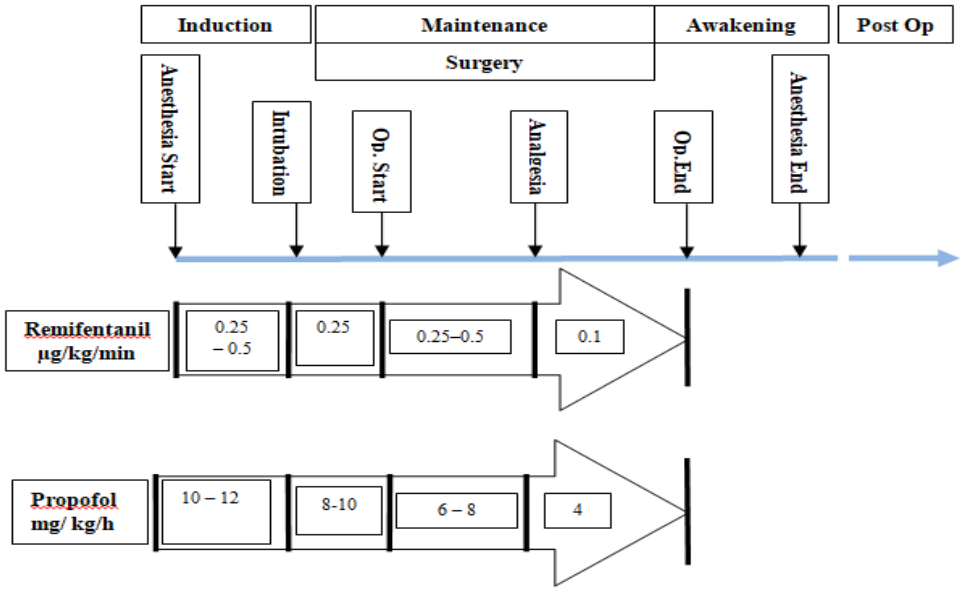

Fig.11. Interaction between Remifentanil and Propofol drug during surgery

During the constant rate of anesthesia or drowsiness the amount of propofol control by decreasing with additional pain-relieving drug eg., nitrous oxide or any other types of opioid drug will not impact on regularly using non-depolarizing drug such as succinylcholine.

a. Advantage

1. The main aim of sedative drug given to the patient is attain by quick and with reduction in nontoxic.
2. It is used for speedy retrieval of patient is obtained by mixing of two drugs comparing to the single drug usage.

Table.5 Arterial Anesthetic Drug effect

Drug	Bolus dose	Infusion rate	Comments
Remifentanil	1 mg/kg	0.05 mg/kg/min	Hypoventilation, sickness, Vomiting, urinary infection
Propofol	2 – 2.5mg/kg	25-75 mg/kg/min	Venous infuriation, pain after injections

VIII. Conclusion

The reaction between Propofol and Remifentanil has its own characteristics in current anesthetic delivery system. If customized DOA monitoring system are anticipate, are depend upon the patient parameters. It can do by uniquely by instigate adaptation technique into feedback control method.At last it is finalized that remifentanil has narcotic / anodyne properties, or that it enhance the anodyne impact of propofol. Compared to the other types of drugs Propofol

and Remifentanil are fewer side effects. The recovery time is very less for these two drugs. It is easily available drug and commonly used in most of the surgery.

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