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General Anaesthetics and Sedatives for Dentistry

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***Abstract*— Sedation and anaesthesia for dental procedure are becoming common and popular amongst patients and dentists. Fear and anxiety are frequent problems in paediatric and also adult patients.**

Different anaesthetic agents have been developed over years the years making the whole process of anaesthesia safe, effective and predictable. They differ considerably based on routes of administration, pharmacokinetics and pharmacodynamics and side effects. The purpose of this review is to study and discuss the various options available for sedation and anaesthesia for dental interventions especially ambulatory surgeries and discuss the recent trends in their use.

***Index Terms*— Nitrous Oxide, Sevoflurane, Dental Anaesthesia, Propofol, Ketamine.**

I. INTRODUCTION

The practice of anaesthesia has evolved overtime, making it safe in majority of the patients. Numerous practice guidelines have been developed over the years to further make it effective and reliable. Dental patients may require general anaesthesia at in-hospital and out hospital settings. Some of the recommendationsare directed for anaesthesia during dental treatment reducing the risk of morbidity and mortality. Multiple anaesthetic drugs have been used to facilitate the whole process of dental surgery. Knowledge of the anesthetic pharmacological agents would further reduce the death and disability.

Conscious sedation as per academy of royal medical colleges in its practice guidelines has been defined as technique leading to a state of depression of central nervous system that allows treatment to be carried out. Throughout the procedure the patient maintains the verbal contact; and drugs and techniques should have wide safety margin enough to render loss of consciousness unlikely. If unconsciousness in form of loss of verbal contact ensues, the patient requires care identical to that of general anaesthesia.[1]

The dental procedures would require a balanced anaesthesia to achieve sedation, amnesia and analgesia, especially in children. In majority of adult patients, infiltration with local anesthetics can easily be done after providing sedation. Multiple agents have been used to achieve the demand of intense analgesia and sedation.

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II. INHALATIONALANAESTHETICS AND SEDATIVES- GASES

A. Nitrous Oxide

Nitrous oxide (N_2O) is a safe and effective sedation technique in dental procedures. N_2O is mixed with oxygen (O_2) in a modern mixer machines and titration is done as per individual patients response. These machines are designed to be used by dentists who provide sedation and perform procedure as well.[2]

N_2O is non irritant, mildly sweet and odorless gas with minimum alveolar concentration 105. Multiple mechanism of action has been hypothesized for nitrous oxide ever since its analgesic properties discovered in eighteenth century.[3]Antinociceptive action of N_2O has been compared with opioids and was blocked by the opioids antagonists naloxone.[4,5]GABAergic, adrenergic, and glutaminergic systems have also found involved in the analgesic actions of N_2O.[6,7]N_2O is believed to activate $GABA_A$ receptor through benzodiazepine site, producing anxiolytic effect.[8] Mechanism of anaesthesia produced by nitrous oxide is poorly understood, however recent evidence suggest the involvement of N-methyl D-aspartate receptor antagonism.[9]

Nitrous oxide is rapidly absorbed into blood from the alveoli during administration. Low blood solubility leads to quick diffusion down the concentration gradient from blood to central nervous system. With cessation of N_2O inhalation, it is rapidly excreted from lungs causing reversal of effects.

Indications for nitrous oxide includes mature and cooperative American Society of Anaesthesiologists Physical Grade (ASA) I and II with dental anxiety, needle phobia and gag reflex.[10,11] It may also be used for management of acute dental trauma and dental extraction. It is widely seen as alternative to general anaesthesia and helpful when other sedation methods are contraindicated. Contraindications for its use are non-cooperative children, nasal obstruction or deformity, chronic obstructive pulmonary disease. Its use is not approved in first trimester of pregnancy, post bleomycin chemotherapy, myasthenia gravis, multiple sclerosis, otitis media and pneumothorax.

N_2O has minimal effects on cardio-respiratory systems providing wide safety margin in dental practices.[12] N_2O is mixed with oxygen in variable concentration during delivery and titration is done through purpose-made mixer system. The titrated gas is administered via special nasal hood placed on patient's nose.Up to 50% N_2O mixed in O_2, generally achieves the desired level of sedation. However infiltration with local anaesthetics may still be required for relatively painful procedures. Inhalation of 100% oxygen prevents diffusion hypoxia at the end of procedure.

The most common side effect after N_2O inhalation is nausea and vomiting and incidence rises with duration of exposure.[13]Rapid diffusion back into alveoli, afterdiscontinuation of administration, causes severe reduction in alveolar concentration of oxygen leading to diffusion hypoxia. The occurrence is more when high concentration of N_2O is used as it is less soluble than oxygen. At recovery, washing out N_2O with administration of 100% oxygen, prevents its occurrence. Administration ofN_2O in conditions like otitis media and pneumothorax leads to expansion of trapped air and causes adverse consequences. This phenomenon of pressure gas effect is due to rapid entry in gas filled space and slow escaped from it. Prolonged exposure of N_2O in health care workers may lead to bone marrow suppression. Nitrous oxide causes inactivation of vitamin B_{12} and changes enzyme methionine synthase, ultimately affects purine nucleotide formation and DNA synthesis.

B. Xenon

It is an inert gas that has unique pharmacological properties such as hypnosis, analgesia, haemodynamic stability, organ protection and lacks toxicity. Xenon has low blood: gas partition coefficient (0.14) leading to shorter recovery time. It was first approved for anaesthesia in Russia in 2000 and later on in all of the Europe. Xenon did not become popular despite all advantages and being termed “ideal anaesthetic”, as it is more expensive than any other anaesthetics.[14]

Xenon has been successfully used as anaesthetic agents for dental interventions without any adverse events.[15] Lazarev et al compared xenon with sevoflurane anesthesia in 103 children in outpatient dental practice, in which 35 children received xenon anesthesia.[16] Stability of diastolic blood pressure and heart rate during procedure and faster awakening at the end of procedure were documented in xenon group.

III. INHALATIONALANAESTHETICS AND SEDATIVES-VOLATILE ANAESTHETICS

Throughout history, multiple volatile anaesthetics including ether and halothane were introduced as anaesthetic agents. However use of those agents was discontinued due to technical difficulties or side effects like nephrotoxicity and hepatotoxicity. Volatile anaesthetics in common practice now a days are sevoflurane, isoflurane and desflurane. These are halogenated methyl-ethyl ether derivatives, non-inflammable, commercially available in liquid form.

Contrary to N_2O, Volatile anaesthetic are used for general anaesthesia for ambulatory and hospital dental procedures. The concentration of volatile anaesthetics is controlled by vaporisers present on modern day anaesthesia machines.

Multiple hypothesis have been presented regarding mechanism of action of volatile anaesthetics.[17]The unitary hypothesis and the Overton rule, nonspecific pharmacology and lipid theoriesare challenged with newer concepts.[18] Molecular actions theories considers volatile anaesthetics interacting proteins (the lipid-free enzyme firefly luciferase and signalling proteins) and ion channels (cysteine-loop neurotransmitter receptors, glutamate receptors and voltage gated channels) leading to inhibition of $GABA_A$ and glycine receptors.[19,20]

A. Sevoflurane

Volatile anaesthetics are increasingly being administered at ambulatory dental surgery as alternative or supplementary to intravenous anaesthetics. Sevoflurane is most commonly used volatile anaesthetic in day care and office based anaesthesia.[21] Fruity and non-pungent nature of sevoflurane, rapid uptake and offset along with minimal effect on cardio-respiratory systems makes it ideal inhalational agents for mask induction especially in children.[22] Emergence agitation,a common occurrence in pediatric patients for dental procedure and associated with rapid awakening, can be reduced with oral ketamine or oral midazolam.[23,24]Confusion may however persist as effects of the sevoflurane lasts longer resulting from slow elimination.

B. Desflurane

Contrary to sevoflurane, desfluraneis pungent in nature and causes severe irritation to pulmonary tissues, making it ineligible for mask induction in dental patients. Very Rapid emergence occurs in desflurane, that has very low blood gas coefficient (0.42) as compared to 0.69 for sevoflurane. It may potentially cause sympathetic stimulation with rapid change in concentration and may lead to tachycardia and prolongation of QTcinterval.[25]Desflurane is more expensive and requires special electric powered vaporizer. Desflurane is used in hospital setting for prolonged surgery and in those patients requiring rapid emergence. Desflurane causes less emergence agitation as compared to sevoflurane despite having low blood gas coefficient.[26]

C. Isoflurane

Isoflurane was introduced in 1980s and has long track record of its use. It is highly potent with lowest minimum alveolar concentration (1.15%). Low material cost and cost effectiveness makes it a preferred choice for maintenance in ambulatory surgeries. Isoflurane is a potent vasodilator and previously considered to cause “coronary steal syndrome”, however recent studies have refuted this claim.[27,28]Isoflurane has been demonstrated to cause ischemic preconditioning leading to cardio and neuro-protection in potentially compromised patients.

IV. INTRAVENOUS ANESTHETICS AND SEDATIVES

A. Benzodiazepines

Midazolam, an imidazobenzodiazepinederivative,is extensively used for minor dental procedure. It has provides sedation, hypnosis, anxiolysis and skeletal muscle relaxation, however lacks analgesic properties.[29] Midazolam and diazepam has faster onset of action, however duration of action of midazolam is shorter. Second peak in plasma concentration and active metabolitemakes diazepam unsuitable for short dental procedures.[30]

Benzodiazepines act upon benzodiazepine (BZD) receptors in the central nervous system, activation of that causes entry

of chloride in neurons and hyperpolarization of the neurons.[31] Nitrous oxide/oxygen mixture during conscious sedation provide analgesia and additive effects.

Midazolam is administered through oral (syrup or tablet) or injectable route (retromolar area) during pediatric dental procedures. Dose adjustment should be considered in patients with hepatic or renal dysfunction. Buccal midazolam may be considered as an alternative to rectal diazepam during seizure attack on dental chair when gaining iv access is difficult.[32] Common side effects of benzodiazepines are respiratory depression and arrest, drowsiness, headache, confusion, nausea/vomiting, syncope, diarrhoea and tremors.[31] Flumazenil is antagonist of benzodiazepine and reverses the effects after overdose.[33]

B. Ketamine

Ketamine, a phencyclidinederivative, produces a state of catalepsy providing sedation, analgesia and dissociative anaesthesia. Mechanism of action of ketamine is through NMDA antagonism. It has been widely employed in outpatient dental anesthesia.[34] Onset of action of ketamine is rapid and smooth, and recovery is predictable.

Ketamine increases sympathetic activity leading to raised heart rate, blood pressure and cardiac output.[35]It should be avoided in tachycardic and hypertensive and patients with coronary artery diseases. Increase in salivary gland secretion and vomiting after ketamine can be prevented by prior atropine or glycopyrrolate administration.[36]Ketamine, during dental procedure, is used in sub-anaesthetic dose and usually supplemented with N_2O/O_2 and benzodiazepine. Oral ketamine, 6mg/kg, provide quick (within 20 minutes), safe and effective sedation in children undergoing ambulatory dental procedures.[37] Earlier oral formulations were less palatable and emetogenic as compared to newer ones that better masks the poor taste of ketamine.[38]

C. Propofol

Propofol(2,6-diisopropylphenol), a potent lipophilic anaesthetic is marketed as 1% propofol formulated in 10% soybean oil emulsion. Initial formulation was in Cremophor El, that caused anaphylaxis in patients.[39]Propofol is administered only intravenously as other routes have very low bioavailability. Propofol potentiates the inhibitory effects of GABA and exerts the hypnotic effects. It binds to the post synaptic $GABA_A$ receptors (β-subunit) that leads to hyperpolarisation of neurons by letting chloride current flow inwards.[40]Although elimination half life is long (2-24 hours), the clinical effects lasts for short duration (30 minutes) due to rapid distribution into peripheral tissues.

Propofol is considered drug of choice for sedation and anaesthesia in day care surgical procedures. However, gaining of intravenous access for its injection in anxious pediatric patients for dental procedure can be challenging. The intravenous access can be acquired by putting the child asleep by inhalation of sevofluene beforehand. Propofol can be administered via target controlled infusion (TCI) pump in subanesthetic doses in anxious adolescent patients requiring dental care.[41]

D. Opioids

Most of above discussed agents donot provide pain relief associated with procedures except ketamine and N_2O. Opioids are added for analgesia along with other sedatives in dental procedures. Fentanyl, commonly used opioids, is administered by intravenous, oral, transdermal and nasal routes. Oral transmucosal, lollipop doses of 0.5-1 mg fentanyl, is more acceptable in children, and produce effective analgesia with mild sedation and negligible respiratory depression.[42]Fentanyl is highly lipophilic and gets absorbed easily through buccal mucosa and skin. Bioavailability is 30-40 % when administered through buccal mucosa due to high hepatic clearance. Recommended intravenous dose is 1mcg/kg, repeated in increment of 1 mcg/kg up to maximum 4mcg/kg. Common side effects are nausea, vomiting, constipation, bradycardia, dose dependent respiratory depression and chest wall rigidity.

Alfentanil, sufentanil and remifentanil are other opioids used in ambulatory surgeries. Alfentanil, rapid and short acting opioid, has less cardiovascular effects as compared to fentanyl and remifentanil, however produces relatively severe respiratory depression. Sufentanil is highly potent (5-10 times fentanyl and 500 times morphine) synthetic opioid and may be used for short procedures especially in heavily opioid dependent or tolerant patients. Intranasal sufentanil has been associated with hypoxaemia and decreased chest compliance.[43]A recent formulation of intranasal sufentanil 0.5 mcg/kg and ketamine 0.5 mg/kg is found effective in pediatric procedural pain management.[44]

E. Dexmedetomedine

It is an imidazole compound, the pharmacologically activedextroisomer of medetomidine, that displays specific and selective α2-adrenoceptor agonism. Activation of postsynaptic α2 receptor in brain and spinal cord produces clinical effects of analgesia, sedation, bradycardia, hypotension and sympatholysis.[45]

Dexmedetomidine has been employed successfully as the primary sedative agent in various dental procedures.[46] Intranasal dexmedetomidine combine with N_2O has comparable safety profile to oral midazolam and N_2O.[47]

Addition of dexmedetomidine as adjuvant to lignocaine, for local injection into oral mucosa, enhances its local anaesthetic property without causing significant systemic side effects.[48]

V. SUMMARY

Dental anaesthesia and sedation has become favoured and fashionable amongst patients and dentists for various dental interventions. Conscious sedation is performed at outpatient setting and improves patient tolerance and acceptability of unpleasant procedures. Complex and prolong dental procedures requires general anesthesia in hospital set up with intensive care. Multiple inhalational and intravenous agents are now available and can be administered alone or in combinationand tailored individually to provide sedative, analgesic and anesthetic effects. Knowledge of these medications and its pharmacological profile and side effects are essential for safe and effects sedation or anaesthesia for dental procedures.

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