Procedural Sedation And Analgesia In Emergency Department: A Review and Update

Surjya Prasad Upadhyay[*1], Ulka Samant[1], Arun Kumar Singh[1], Hemchander Sundararaj[2], Malini Rao[3], Piyush N Mallick[4]

[1]*Specialist Anaaesthesiology, NMC Hospital, Dubai Investment park, Dubai, United Arab Emirates.*

[2]*Specialist physician, Emergency medicine, NMC Hospital, Dubai Investment park, Dubai; United Arab Emirates.*

[3]*Consultant Anaesthesiologist, BR Medical Suites. Dubai; United Arab Emirates.*

[4]*Consultant Anaesthesiologist, Al Zahra Hospital Sharjah, United Arab Emirates.*

[*]**Corresponding author**
Surjya Prasad Upadhyay, Specialist Anaaesthesiology, NMC Hospital, DIP; Dubai Investment park, Dubai; United Arab Emirates, Tel: +971-554078445; E-mail: surjya.upadhyay@nmc.ae

Abstract
Procedural sedation and analgesia is one of the common clinical practice in the emergency department. The level of sedation must be adjusted in such a way that the it allows patient to tolerate unpleasant procedures while maintaining normal physiologic reflexes and consciousness and able to understand and respond to verbal or light tactile stimulus. Although drugs used for procedural sedation has wide margin of safety but inappropriate monitoring or dosing may cause serious adverse events. Procedural sedation in emergency department is not without risk. Proper monitoring; provision of readily available access to resuscitation facility and continuous presence of trained staffs capable for airway management and providing advanced life support measure contributes reduction in adverse outcome. Pre-procedural evaluation is done to screened for suitability for procedural sedation and assess the risk factors. Patients with full stomach, difficult airway or significant medical illness requiring more than mild sedation, alternative to procedural sedation should be consider. Clinician performing procedural sedation should have through knowledge of action, dose, side effects, antidote of commonly used sedative analgesics. Newer and innovative techniques have been evolved recently including transmucosal, transnasal, inhalational anaesthetic, patient controlled sedations, target controlled sedation. All patients after procedural sedation should be monitored in a designated recovery area and should not be discharged until they meet all the discharge criteria and while sending home, proper written discharge instruction should be provided to all.

Keywords: Procedural sedation and analgesia, Conscious sedation, Emergency procedure, Procedure outside operating room.

Introduction

Use of procedural sedation and analgesia is one of the common clinical practice in the emergency department. Effective use of procedural sedation not only alleviate pain and suffering and alloy anxiety for patients during diagnostic or therapeutic procedure, but also enhances the performance of these procedures. Procedural sedation is also described as conscious sedation. Stages of sedation is a continuum from minimal or mild sedation, moderate sedation, deep sedation to fully unconsciousness which is consistent with general anaesthesia where all protective reflexes get lost [1-3]. The likelihood of adverse events increases with increasing the depth of sedation.

Procedural sedation is defined as "a technique in which the use of a drug or drugs produces a state of depression of the central nervous system enabling treatment to be carried out, but during which verbal contact with the patient is maintained throughout the procedure." The drugs and techniques used to provide procedural sedation should carry a margin of safety wide enough to render loss of consciousness unlikely [3-6]. Conscious sedation is popular and widely uses term, but it is a misused or vague term as the level of sedation at per definition of conscious sedation by American Association of physician (AAP) in 1985 is insufficient for most painful procedures, especially in children [7].

The level of sedation must be adjusted in such a way that it allows patient to tolerate unpleasant procedures while maintaining normal physiologic reflexes and consciousness and able to understand and respond to verbal or light tactile stimulus. Current definition of

moderate to deep sedation is considered as gray zone. Procedural sedation in uncooperative children is another aspect and is often not covered by standard definition and guidelines. One of the important aspects for certain procedure is absolute immobility and for such children the key to success is inducing sleep. The term sleep sedation or safe sleep was evolved and defined as the patient is not easily roused with a safety margin wide enough to render the loss of airway and breathing reflexes unlikely [8]. Although drugs used for procedural sedation has wide margin of safety but inappropriate monitoring or dosing may cause serious adverse event. Goals of procedural sedation and analgesia are to minimize physical pain and discomfort, maintain patient safety and welfare, control anxiety, minimize psychological trauma and to provide maximum amnesia.

Definitions
The American Society of Anesthesiologists (ASA) describes two broad class of sedation; non-dissociative and dissociative; the non-dissociative is sub classified into four levels based on depth of sedation- from minimal sedation to general anaesthesia- in addition to dissociative sedation [9]. In practice, prolonged deep sedation or general anaesthesia is rarely used in the emergency department in the absence of a clinician with appropriate training in anaesthesia.

Procedural sedation and analgesia
Technique of administering sedative or dissociative agents with or without any analgesic to induce an altered state of consciousness to allow the patient to tolerate unpleasant or painful procedures while preserving cardio-respiratory function [3].

Minimal or mild sedation and analgesia
Essentially mild anxiolysis or pain control with near-baseline level of alertness. Patients respond normally to verbal commands, although cognitive and coordination might be impaired. Example of appropriate use: changing burns dressings.

Moderate sedation and analgesia
It is deeper level of sedation than mild sedation; patients are sleepy but easily aroused by verbal or tactile stimuli. Although their airway and respiration and cardiovascular functions are usually maintained, these may be suppressed with deeper levels of sedation (which is a continuum). Moderate level sedation exhibit slurred speech, delayed response to verbal stimuli and may have amnesia also. Example of appropriate use: direct current cardio version.

Deep sedation and analgesia
Patients require painful or repeated stimuli to evoke a purposeful response. Airway or ventilator support (or both) may be needed. Cardiovascular function is usually maintained but not assured. Example of appropriate use: major joint reduction (dislocated shoulder reduction).

General anaesthesia: patient has no purposeful response to even repeated painful stimuli. Airway and ventilator support is usually required. Cardiovascular function may also be impaired. Not appropriate for general use in the emergency department except during emergency intubation.

Dissociative sedation
Dissociative sedation is described as a trance-like cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respiration, and cardiopulmonary stability. Ketamine is the commonly used agent to induce dissociative state. Example of appropriate use: fracture reduction (distal radius fractures in young adults)

Risk and problem in procedural sedation
Unlike operative room or other area; the emergency department is a unique environment where patients arrive anytime on unscheduled basis and often with challenging medical problems which may require prompt interventions to stabilization or prevent further deterioration.

Major unique challenges with anaesthesia outside operative room include those related to patient, procedure and environment. Physician unfamiliar with the anaesthesia outside operative room tends to underestimate the fact that patients undergoing procedure that require newer and advanced technological equipment are at higher risk [10]. Unfamiliar location, inadequate monitoring, insufficient or untrained staff and non-availability of emergency resuscitation equipment or medication in emergency situations place both emergency physician and patients at risk.

Clinician involved in procedural sedation must understand the nature of the procedure, invasiveness, positioning and duration for the procedure and will formulate the plan in advance in liaise with proceduralalist including contingencies for emergencies and adverse outcomes. Nursing and technical staff involve in procedural sedation must be trained to assist or carry out immediate cardio-pulmonary resuscitation. American Society of Anesthesiology (ASA) has provided minimal guidelines for anesthesia in the nonoperating room to improve the quality of patient care [11].

Each location should have
- Reliable source of oxygen adequate for the length of the procedure, with a backup supply - Adequate and reliable source of suction - Adequate and reliable system for scavenging waste anesthetic gases - Self-inflating hand resuscitator bag capable of administering > 90% oxygen - Adequate anesthesia drugs, supplies, and equipment for the intended anesthesia care - Adequate monitoring equipment to allow adherence to the "Standards for Basic Anesthetic Monitoring" - Sufficient electrical outlets to satisfy anesthesia machine and monitoring equipment requirement
Provision for adequate illumination
- The patient, anesthesia machine, and monitoring equipment - Battery-powered illumination other than a laryngoscope immediately available

Sufficient space
- Accommodate necessary equipment and personnel - Allow expeditious access to the patient, anesthesia machine, and monitoring equipment
Immediate availability of an emergency cart
- Defibrillator, emergency drugs, and other equipment to provide cardiopulmonary resuscitation
Staff
- Trained clinician in advanced life support - Adequately trained supporting staff
Appropriate post-anesthetic management
- Adequate number of trained staff - Appropriate equipment available to safely transport the patient to a post-anesthesia care unit

Table 1: ASA Guidelines for Non-operating Room Anesthesia.

Complications in procedural sedation can be varies from mild difficulties to fatal one. Serious complication attributable to procedural sedation and analgesia rarely occur. Adverse outcomes may include cardio-respiratory depression (hypoxia, hypercarbia, hypotension, tachycardia), nausea vomiting, aspiration, emergence reactions, anaphylaxis, inadequate sedation preventing completion of the procedure [12]. Significant respiratory compromise develops in well less than one percent of cases. Incidence of complications may be higher in non-operative room sedation than operative room. When procedure sedation is conducted by non-anaesthesiologist outside operative room, incidence of complications may not be different, but the rate of death and failure-to-rescue were greater when care was not directed by anesthesiologists, demonstrating that 30-day morbidity and mortality were lower when anesthesiologists directed anesthesia care [14]. Most of the complications during procedural sedation can be preventable through proper preprocedural evaluation, appropriate monitoring and judicial use of sedative analgesic medications. Particular attention should be paid to difficult airway where oxygenation and ventilation may be difficult, also patients with full stomach, should the need for airway management arise. Such patients may not be appropriate candidates for PSA.

Example of some common procedures in emergency department Requiring sedation [13]
- Cardioversion in a conscious patient
- Closed reduction of simple fracture/dislocation
- Wound dressing/ suturing
- Simple abscess drainage
- Control of intoxicated patient
- Diagnostic procedure in uncoperative patient/ children
- Chest tube insertion
- Foreign body removal
- Diagnostic procedure like lumbar puncture, arthocentesis, bone marrow biopsy, radiology evaluation

Preparation of Patient before procedural sedation
A health care provider with current privileges to administer sedation-analgesia must conduct a pre-procedural evaluation.

Detail history, cognitive functions, physical examination, airway assessment should be done on this pre-procedural assessment. As such there are no absolute contraindications to procedural sedation and analgesia. Relative contraindication may include extreme of age, significant medical illness and known or anticipated difficult airway. Fasting is not pre-requisite and does not appear to have a major impact on aspiration risk for procedural sedation and analgesia limiting only mild to moderate sedation [15,16]. Addition of sedation and analgesia introduces an independent risk factor for morbidity and mortality apart from the risk due to procedure itself [3]. Before proceeding with emergency room procedural sedation certain factors must be considered, the patient and clinician must agree that the benefit outweigh the risk of procedural sedation analgesia. As such the risk depends on patient's clinical condition and nature of the procedure. Patients with significant cardio-respiratory disease are at increased risk for complications during procedural sedation. Important comrobidities include heart failure, ischemic heart disease, chronic obstructive airway disease, neuromuscular disease, significant renal impairment etc [11,17,18]. Unfortunately, there is no robust evidence that such patients may benefit from other approach (monitor anaesthesia care, general anaesthesia in the operating room). To reduce the risk and major complications in patients with major co-morbid condition and in elderly; a more conservative approach or modification of procedural sedation technique can be done such as lower rate of drug administration and slow titration. Patient with known or anticipated difficult airway (especially those with difficult to ventilate) should respiratory difficulty arise while the patient is sedated should not be taken for emergency room procedural sedation and should be considered for alternative to procedural sedation such as performing procedure in operating room under supervision of anaesthesiologist. (Monitor anaesthesia care/ GA/ awake fiberoptic intubation).

Patients undergoing procedural sedation in emergency room are thought to be at increased risk of aspiration as most patients will not be properly fasted state and their stomach are often full. Aspiration of gastric content above a critical volume and acidity can cause severe respiratory and systemic consequences [19]. Although, American Society of Anaesthesiologist (ASA) has given a clear guideline for preprocedural fasting for patient undergoing elective procedure under sedation or general anaesthesia. ASA recommends minimum fasting of 2 hours after drinking clear fluid, 4 hrs after breast milk and 6 hrs after formula feed or solid [2]. Implementation of this guideline in emergency department is not always practically possible. Most patients do not meet the fasting requirement and the most of the procedure are of emergent nature and cannot be delayed. The importance of fasting in emergency room for preventing aspiration during procedural sedation remains unclear [20-24].

So far, we don't have clear evidence to show a relationship among fasting time, gastric volume and acidity, depth of sedation and likelihood of aspiration. Clinically, it is very rare to have significant aspiration of gastric content during emergency procedural sedation [15]. Endotracheal intubation may not protect from aspiration,

aspiration can occur despite the presence of an endotracheal tube. American College of Emergency Physician policy statement of procedural sedation analgesia states "Recent food intake is not a contraindication for administering procedural sedation and analgesia but should be considered in choosing the timing and target of sedation" [3]. To reduce the risk of aspiration, following approach may be appropriate for emergency procedural sedation.

- It is always better to carefully consider the risks and benefit of performing a procedure in emergency. It is reasonable to wait if the patient is full stomach and the procedure is not a true emergency specially when a potential risk of aspiration or a potential difficult airway exist [23,25] (bowel obstruction, extreme of age, depressed mental state, trauma).
- Avoiding deeper level of sedation: although, no evidence exist that deeper level increase the risk of aspiration. However, light level of sedation permit patient to maintain protective airway reflexes [23].
- No role of pre-procedural antacid or motility agents in reducing aspiration risk in emergency procedural sedation [26].

Patients undergoing deeper level of sedation where verbal contact might be lost; it is better to adhere to fasting guideline of ASA (2 hrs for clear fluid, 4 hrs for breast milk and 6 hours for formula or solid) [9].

Consent
Valid Consent is an absolute requirement for all patients requiring sedation. The rules and regulations vary around the world. Regardless of Geography, Sedation, and all possible adverse effects of Sedation, must be completely explained in a manner comprehensible to the patient, or in the case of a Minor - his Legal Guardians / Parents.

Pre-requisites and personnel
The choice of personnel chosen to administer sedation is varied and maybe administered safely by other clinicians, including emergency and critical care physicians and nurse specialists [27]. Whoever is performing the procedural sedation; he/she have in-depth knowledge of the relevant medication (action, side effect, reversal) and should be well versed in advanced cardiovascular life support (ACLS) including skill of airway managements. Number of personnel needed for any procedural sedation may vary according to the patient and the procedure. Minimum of one clinician performing procedure and one nurse administering sedative analgesic and monitoring and recording patient's clinical status and vital signs may be suffice for simple procedure [24]. Serious adverse event can still occur after any procedural sedation, as per ASA guideline there must be someone with advanced life support skill to be immediately available (within 5 min) if need arises [9]. It remains controversial whether a separate clinician who is skilled in deeper sedation and airway management should also be present apart from the clinician performing the procedure in the emergency room [3,18]. Hogan et al. in a prospective observational study involving procedural sedation performed by single emergency physician (EP) had comparably similar high success rate with low

complications when compared with procedural sedation performed by EP along with a nursing staff [28]. Each hospital should have their policy guideline and the accreditation for sedation practice within the emergency department. The director of the emergency department responsibility to provide the approval status to non-specialist medical staff to perform the procedural sedation. The sedation accreditation is suggested for all clinician engaged in procedural sedation in emergency department.

Monitoring and equipments
Basic monitoring should be of same standard basic monitoring as in operating room. Close claims in cases with adverse events during procedural sedation frequently judged as substandard monitoring [12]. The Location of the Sedation must be checked and made familiar by the Seditionist before the case. Suction, airway equipments of appropriate size, provision for positive pressure ventilation device, intravenous equipments, pharmacologic antagonist and basic resuscitative medication should always be available before proceeding with any level of sedation [9]. Staff must be trained to observe the vital signs of the Sedated patient and react in an appropriate way for Sedation. Continually evaluating and monitoring respiratory and circulatory requirements prior to, during, and following the procedure is essential. Continuous electrocardiography and capnography monitoring should be done in cases involving moderate to deep level of sedation, during prolonged procedure or in high risk patients. Close observation for patient appearance, airway patency and response to stimuli (verbal, tactile) are essential part of monitoring during procedural sedation [2,9,29]. Supplemental low level of oxygen does not reliably prevent hypoxia, may in fact delay the detection of hypoventilation during procedural sedation in patients without capnography monitoring [30-33]. Supplemental oxygen (high flow) should be given to patients at higher risk or deeper level of sedation or procedure lasting longer duration.

Physical plant	Environment	Monitors	Transport capability
Oxygen and backup	Anesthesia machine	Oximetry	Oxygen delivery
Wall gases	Oxygen delivery	Capnography	Oxygen tanks
Suction	Suction catheters	Blood pressure	Portable monitors
Visual access	Intubation equipment	Temperature	
Thermostatic control	Intravenous pumps	ECG with Defibrillator	
Electrical outlets			

Table 2: Monitors and Equipment for Non-operating Room Anesthesia.

Techniques for sedation
There is range of techniques available for procedural sedation. Whatever the technique is used, the selection of technique must be appropriate for the individual patient and procedure and not chosen simply for operator or sedationist convenience or at the insistence

of a third party. Use of sedative medication should not negate the need for good communication and behavioral management. Adopting the principle of minimal intervention, the simplest and safest technique that is likely to be effective based on patient and clinical need should be used.

Titration of sedative medication is very important in term of safety and effectiveness. Both over-sedation and under sedation have adverse effect on the patient and delivery of the effective treatment. As a general role single drug is easy to titrated, combining multiple drugs may produce synergistic effects, have different timing for onset and peak effects and sometime unpredictable and difficult to titrate rendering safety margin narrowed, increasing the likelihood of overdose and cardio-respiratory depression. Another important issue is avoiding very strong sedative drugs with narrow therapeutic indices and reduced margin of safety potentially increasing the likelihood of adverse events. While sedating a patient, care must be taken when combining intravenous medications which might leads to pharmaceutical synergy, with enhanced clinical effects, and consequent narrower margins of safety. In all cases, intravenous sedation is only to be administered by experienced practitioners in justifiable documented cases in a safe approved setting, using routine ASA monitors in all cases, in a facility fully equipped with backup safety measures.

Inhalational Nitrous Oxide with Oxygen
Nitrous Oxide is the oldest inhalational agent used to sedate Dental Cases, labor analgesia and many other surgical procedures. It is odorless, tasteless, ultra short acting (near immediate onset) gas with moderate analgesic, anxiolytic and sedative properties. When combined with Oxygen, Nitrous Oxide provides excellent Analgesia, Anxiolysis, and light Anesthesia. It is commonly delivered in an appropriate nasal mask in Oxygen at concentrations of 40% - 70% [34]. It is well tolerated by all age groups, main disadvantages tolerance developed very fast, room where it is used must be well-ventilated with a scavenging system to prevent exposure to others, and it is not a very strong analgesic for more painful procedure like closed reduction of fractures. It is incapable of producing deep sedation or general anaesthesia unless combined with other inhalational / intravenous sedative agent. As with of intravenous sedative agents, nitrous oxide should be administered only with standard protocol, the delivery device must employ specific safety features such as prevention of hypoxic mixture and use of pulse oximetry [34-36].

Intravenous sedation/analgesia
Various drugs available to provide procedural sedation depending on the invasiveness, duration of procedure, facilities for monitoring and resuscitation and expertise of the personnel involved in the sedation process. The greatest threat to the safety of intravenous sedation is airway compromise, loss of airway reflexes and risk of aspiration particularly in emergency procedure and hemodynamic instability. To reduce the risk of cardio-respiratory compromise it is very essential to identify high-risk patient, appropriate selection of medications, and adherence to dosing recommendation, appropriate intraprocedural monitoring and prompt intervention

when adverse effects are recognized [37]. Commonly used IV sedation either alone or combination of other IV sedative/ analgesic are described as below.

Benzodiazepines (BZD)
Benzodiazepines provided number of favorable effects such as anxiolysis, amnesia, sedation and anticonvulsive effects. BZD binds to receptor sites in the Gamma Amino Butyric Acid (GABA) system, which facilitate the binding of GABA to its receptor and potentiates GABA-mediated chloride influx and resulting GABA-nergic actions. The BZD can have adverse effects on respiratory and hemodynamic function. Midazolam is commonly used BZD because of faster onset, less pain on injection, water soluble, more reliable amnesia and shorter duration of action. As BZD lack any analgesic action, it is often combined with opioid, generally fentanyl which resembled in pharmacokinetic profile (rapid onset, duration and offset). BZD has good anxiolysis and amnestic action but no analgesia as such. It can be used as sole agent for mild sedation or combined with opioid or other agents for moderate to deep sedation. It has onset time of 2-5 min after intravenous administration with duration ranging from 30 to 60 min. typical adult dose of midazolam is 0.02-0.1 mg/kg IV initially; if further sedation is required, may repeat with 25% of initial dose after 3-5 min; not to exceed 2.5 mg/dose (1.5 mg for elderly persons) and 5 mg cumulative dose (3.5 mg for elderly persons) Of note, concomitant use of fentanyl and midazolam have synergistic action and reduces the requirement of each other. Midazolam can be administered by various routes including oral, nasal, buccal, transmucosal, intramuscular and intravenous ones [35,37,38].

Propofol
It is a potent intravenous anaesthetic agent, because of its unique pharmacologic profile of rapid onset, reliable sedation, rapid recovery and lack of active metabolite has accounted for its popularity in the arena of procedural sedation. Often used in sub-anaesthetic dosage to provide procedural sedation in various procedures outside the operative room. There is no analgesic action of protocol and is associated with number of side effects such as pain on injection, rapid attainment and overshoot of depth of sedation than intended. Onset of action is very rapid with peak effects at 90-120 sec with duration of action range from 5-10 min depending on the dose. Typical dose 0.5-1 mg/kg IV loading dose; may repeat by 0.5-mg/kg increments 3-5min. Main drawback: It causes hypotension (due to myocardial depression) and respiratory depression. It should be avoided in patients with severe medical problem where there is risk of hypotension that can produce serious complication (sepsis, hypovolemia, cardiac dysfunction). For moderate to deep level of sedation, it is combined with either short acting opioid or with ketamine [39-45].

Ketamine
Ketamine causes profound analgesia with dissociative and amnestic action. It has strong analgesic action even at sub-anaesthetic dose and with this dose it does not impair upper airway reflexes and thus allowing patient to breathe spontaneously and maintain the protective reflexes. However, though the reflexes may

remain intact but cannot be assume to be protective [46]. Ketamine has dosed related side effects notably increased muscle tone, may cause rigidity, increase in blood pressure and may results in a dissociative state where patient may not be able to speak or respond purposefully to verbal commands. With increasing doses it frequently causes emergence delirium described as vivid imaginary, hallucinations, confusion, excitement, irrational behavior etc which may last from 1-3 hours. Reported side effects of ketamine include tachycardia, hypertension, laryngospasm, and emergence delirium, hyper salivation, increased in intraocular, intragastric and intracranial pressure. Excessive salivation can be avoided by using antisialogogue. Avoid stimulation of oropharynx with suction device or other instruments in patients receiving ketamine as excessive stimulation of oropharynx can trigger laryngospasm. Dose of ketamine for procedural sedation and analgesia: IV 1-2 mg/kg loading dose followed by 0.25-1 mg/kg IV 10-15min; administer slowly, not to exceed 0.5 mg/kg/min. Intramuscular: 2-5mg/kg/dose. Oral: 6-10 mg/kg/dose PO mixed in cola or other beverage 30 min before procedure. Incidences of delirium and other side effects can be minimized by limiting the dose of ketamine or using it in conjunctions with other sedative hypnotic. Commonly used combination medications with ketamine are midazolam, propofol and dexmedetomidine [46-52].

Etomidate
Etomidate is an imidazole, ultra short acting sedative with minimal cardiac depressant is one of the commonly used medication for emergency procedural sedation because of cardiac stability. For procedural sedation it is given IV at dose 0.1 mg-0.15 mg/kg over 30 -60 sec and can be repeated after 3-5 min. onset of action is less than 30 sec and duration of effect 5-15 min [53,54]. It has no analgesic action and requires co administration of opioid, common side effects include; myoclonus and pain on injection, respiratory depression, nausea and vomiting and lowering of seizure threshold. Main drawback of etomidate is that it causes adrenal suppression, although no clinical significance unless repeated dosed or used for prolonged period [55-57].

Opioids
Opoids mediate analgesics and dose dependent sedation by acting on both Mu and Kappa opioid receptors. However, the degree of sedation using opioid as sole agent is less intense and unpredictable than that of other sedative-hypnotic. Moreover, high dose opioid are associated with respiratory depression and can occur with any opioid which is dose-dependent and related to the potency of the opioid chosen [58]. In addition sedation and respiratory depression, another respiratory effects is chest wall rigidity which is more common with newer synthetic opioid specially when administered rapidly in large doses and perhaps more common in younger patients [59,60]. Longer acting opioid such as morphine, pethidine are certainly not the agent of choice for procedural sedation because of slower onset and longer duration of action. Shorter acting opioid like fentanyl, alfentanyl sufentanil are often used as analgesic component along with other sedative agent for painful procedural sedation. When used with other sedative agent it has synergestic action and can cause sedation, respiratory depression or hypotension. Unlike the analgesic effects of opioids which follow a fairly consistent dose-response, the sedation and other side effects do not always follow this pattern and higher doses invariably lead to unpleasant side effects like as nausea and vomiting [61]. Fentanyl: Rapid onset of action, 75-125 times potent than morphine, given at dose of 0.5-1 mcg/kg slow IV push (over 1-2 min); may repeat every two minutes until appropriate level of sedation and analgesia is attained. It is frequently used in combination with other sedative mostly midazolam, propofol [35].

Alfentanil
Alfentanil can be used as sole agent or in combination with other sedative for painful procedural sedation. Can be given at dose of 2.5-5 mg/kg and can be repeated every 3-5 min. Higher doses of alfentanil may be associated with minor respiratory complications requiring interventions [62].

Coadministration of midazolam and fentanyl
Combination of midazolam and fentanyl is one of the commonly used medication for emergency procedural sedation. Midazolam alone has very minimal risk of significant respiratory depression, when combined with fentanyl; it can cause hypoventilation, respiratory obstruction needing interventions. Midazolam is relatively slower acting and longer duration than fentanyl, so to get maximum synergism, midazolam be given first and then fentanyl titrated carefully thereafter. Regardless of drug order, clinician must titrate these medication very carefully [3,35,63].

Ketofol
Combination of ketamine and propofol is often called ketofol is a potential alternative for procedural sedation, they are mostly combined together in same single syringe and are physically compatible for 1 hr at 23 degree C [64]. A number of studies have demonstrated that the varying proportion of combination in ketofol (1:1 to 1:10 by weight) for sedation is safe and effective. The combination of the two agents appears to reduce side effects of each medication used alone, and allows for a rapid recovery time [50,51,65-68]. The optimal ratio of ketamine to propofol in ketofol has not been defined yet. Higher ketamine proportion tends to cause more psycho-mimetic effects while higher propofol may cause more cardiac-respiratory depression. Coulter et al. conducted a dose simulation study using 1:1 to 1:10 ketamine to propofol ratio combination for procedural sedation in pediatric and young adults (2-20 yrs). A ketamine-to-propofol ratio of 1:3 was the best combination for intermittent dosing. Ratio greater than 1:3 resulted delayed recovery. They suggested ketamine to propofol of 1:3 for boluses during short procedures (5-20 min) and 1:4 ratio for short infusion as an alternative to intermittent boluses [69]. Many studies to date failed to show that use of ketofol is more effective and safer than use of either agent (propofol or ketamine) alone for procedural sedation in adults [51,67-70].

Dexmedetomidine
Dexmedetomidine is a selective alpha 2 agnosit and has anxiolutic, sedative, analgesic and sympatholytic and reduces anaesthetic requirements [71]. It has been used for procedural sedation in both

pediatric and adult patients. It is a sedative with no or minimal respiratory depression, antisialogogue, does not cause tachycardia or hypertension, easily arousable with clear mind [72-74]. Limited data on adult population undergoing procedural sedation with dexmedetomidine has shown it to efficacious and safe with sufficient analgesia but limited amnesia and prolonged recovery time [75-78]. Although generally effective for sedation for noninvasive and short procedure, dexmedetomidine as sole agent has not been uniformly successful for invasive procedures [79-83]. It is slowly losing the popularity as sole agent for procedural sedation due to its slow onset, delayed recovery, minimal analgesia and limited amnesia. However, there is growing interest in combination of dexmedetomidine with ketamine because of anecdotal experience and few series of studies demonstrate the utility and rationale for combination therapy. When used together, dexmedetomidine may limit the tachycardia, hypertension, salivation, and emergence phenomena from ketamine, whereas addition of ketamine speed up the sedation process and may prevent the bradycardia and hypotension that has been reported with dexmedetomidine [84-86]. Various regimens have been reported in the literature, the most common regimen appears to be the use of a bolus dose of both agents, dexmedetomidine (1µg/kg) and ketamine (1-2mg/kg), to initiate sedation followed by a dexmedetomidine infusion with supplemental bolus doses of ketamine as needed. Combination of ketamine and dexmedetomidine may be more appropriate for procedural sedation in patients with compromised respiratory or cardiac function. When compared with other agents used for procedural sedation, these two agents have limited effects on ventilatory function when compared with other more commonly used agents [52,87,88].

Adjuncts
Many adjuncts can be used in emergency room to reduce or eliminate the dosage requirement of sedative analgesic. With the advancement in knowledge of ultrasound many peripheral nerve block or regional nerve block can be safely performed in emergency room which obviate the need for moderate to deep sedation [89]. Hematoma blocks can be used in patients with long bone fracture which also decreased the requirement of strong sedative analgesics for manipulation of fracture [90].

Special consideration
Patient at risk of hypotension, elderly, multiple co-morbid condition, pediatric and pregnancy are at higher risk for adverse outcome related to procedural sedation and due attention must be paid in drug selection and proper monitoring.

Patients at risk of hypotension
Emergency physician must carefully evaluate the risk and benefit for going ahead with any procedural sedation in patients with increased risk of complications. Patients with septic shock; hypovolemia due to dehydration or volume loss, presence of cardiac disease or some other condition, it is better to use drug which causes less cardiovascular depression; either ketamine, etomidate or short acting opioid be used for procedural sedation.

Patients at risk of airway or respiratory complications
Patients with known difficult or anticipated difficult airway or where the airway obstruction is anticipated or patients with compromised respiratory function, ketamine is the drug of choice unless contraindicated as it does not cause respiratory depression, increases neck muscle tone to keep airway patent and maintained protective airway reflexes.

Pediatric consideration
The choice and selection of agent for pediatric procedural sedation differ slightly with development of technology and better pharmacologic profile of modern drugs in new ways with high success. Newer alternate routes has been proposed and investigated such as transmucosal (intranasal, buccal, sublinguial) which has much less discomfort than intravenous route with faster and predictable action than oral sedation. Midazolam is the most frequently used sedative agent in pediatric and can be administered via various route (oral, nasal, rectal, intramuscular, intravenous). It provides excellent anxiolytic and amnesia. It can be safely combined with intranasal fentanyl. Another agent frequently used in paediatric is ketamine which can also be given through various routes [91-94]. Propofol and dexmedetomidine is also being increasingly used in paediatric procedural sedation. Dexmedetomidine can also be administered through buccal, intranasal or oral route [95].

Unlike adult patients, pediatric patients require careful preoperative evaluation and intraoperative monitoring during the procedural sedation as most of the patient in this group require moderate to deeper level of sedation which may compromise the cardio-respiratory mechanics. Many pediatric patients may actually land up into general anaesthesia; pediatric patients should be prepared and proper fasting guideline to be adhered as if they are going to have full general anaesthesia.

Pregnancy
Sedation is generally avoided in pregnant patients, in exceptional cases such patient can be taken up for procedural sedation with proper precaution [96].
- Gastroprophylaxis: pre-procedural administration of prokinetic (metoclopramide) to reduce gastric content and decreased stomach acidity (H2 antagonist, proton pump inhibitor, sodium citrate) may reduce the risk of vomiting and aspiration.
- Pre-procedural hydration and left lateral displacement of uterus- to reduce the risk of hypotension due to aorto caval compression. Fetal monitoring is not required but should be considered for women in the third trimester.
- Oxygen supplementation to counteract the risk of sedation-related maternal desaturation.
- Any potential teratogenic drug should be avoided.

Specific Advice
Patients in pain: Any patients in severe pain should be provided with adequate analgesia before proceeding to sedation. Intravenous route is the preferred and most predictable method for providing

analgesia in emergency set up. Local factors such as availability of medication, familiarity and clinical experience of the emergency staff will determine the drug choice as will safety, effectiveness and cost factor [5,97].

Post procedural care and discharge

As sedation is stimulus-dependent, at the end of the procedure as there is no stimulus, patient is likely to become more sedated than during the procedure itself. This can lead to hypoventilation and hypoxia in susceptible patients (extreme of age, patients with cardio-respiratory disease). After the completion procedure, it is important to keep monitoring and recording the vital sign, medications, fluid until the patient responds to verbal or tactile stimulation.

Many patients (based on clinical condition) are directly discharged from the ED after diagnostic or therapeutic procedure. To assure that these patients are discharge home safely and efficiently, they must meet discharge criteria before being sent home. It is not uncommon for patients to experience mild symptoms, such as nausea, lightheartedness, fatigue, or unsteadiness for up to 24 hours. Serious adverse events, such as hypoxia, rarely occur after discharge. This should be made clear to the patient.

In general, discharge criteria should include [98]
- Protective reflexes are intact and the patient exhibits no signs of respiratory distress
- Vitals sign should be within 15% of preprocedural value.
- Patient should be awake, alert and responds to commands appropriate to age.
- Able to sit upright or ambulate with assistance without hypotension.
- No pain or minimal pain that can be controlled with simple analgesics.
- No active bleeding. Should not be actively vomiting and nausea if any should be mild.
- A minimum of 30 minutes has elapsed since the end of the procedure; and
- The patient is accompanied by a responsible adult.
- Post-discharge instruction- should be given in writing in clear and understandable language by the patient or caretaker.

Summary and Recommendation

A properly administered procedural sedation not only allows painful procedure to be performed, it increases the performance time and success of any procedure.

Sedation level is subclassifed into mild, moderate, deep sedation and general anaesthesia. Most emergency procedure requires mild to moderate sedation and analgesia. Whenever deeper level of sedation or GA is intended, it is always safer to involved clinician with more advanced skill in airway and resuscitation (anesthesiologist). All personals involved in procedural sedation must have knowledge of advanced life support measure and airway management. Adequate equipment, monitoring and resuscitation facility must be there whenever procedural sedation is conducted.

Proper patient evaluation; specially the co-morbid medical conditions, fasting status and risk of aspiration and airway evaluation should be meticulously done and recorded. Adopting the principle of minimal intervention, the simplest and safest technique that is likely to be effective based on patient and clinical need should be used. Choice of technique or sedation depends patient type, invasiveness and length of the procedure and presence of co-morbid conditions.

Ideal drugs for procedural sedation should have a rapid onset and short duration of action, maintains hemodynamic stability, and do not cause major side effects. Several medications are commonly used but till date, no single drug is ideal for all situations. All patients after procedural sedation should be monitored in a designated recovery area and should not be discharged until they meet all the discharge criteria and while sending home, proper written discharge instruction should be provided to all.

References

1. Academy of Medical Royal Colleges (2013) Safe Sedation Practice for health care Procedures. London. AoMRC.
2. American Society of Anesthesiologists (2004) Continuum of depth of sedation definition of general anesthesia and levels of sedation/analgesia.
3. Godwin SA, Caro DA, Wolf SJ (2005) American College of Emergency Physicians. ACEP clinical policy: procedural sedation and analgesia in the emergency department. Ann Emerg Med 45: 177-196.
4. National Institute for Health and Care Excellence (2010) Sedation in Children and Young People. London: NICE.
5. Atkinson P, French J, Nice CA (2014) Procedural sedation and analgesia for adults in the emergency department. BMJ 348: g2965.
6. From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Procedural Sedation and Analgesia: Clinical Policy: Procedural Sedation and Analgesia in the Emergency Department (2014) Annals of Emergency Medicine 63: 247-258
7. Guidelines for the elective use of conscious sedation, deep sedation, and general anesthesia in pediatric patients (1985) Pediatr Dent 7: 334.
8. Sury MR, Hatch DJ, Deeley T, Dicks-Mireaux C, Chong WK (1999) Development of a nurse-led sedation service for paediatric magnetic resonance imaging. Lancet 353: 1667-1671.
9. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists (2002) Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 96: 1004-1017.
10. Youn AM, Ko YK, Kim YH (2015) Anesthesia and sedation outside of the operating room. Korean J Anesthesiol 68: 323-331.
11. Miller MA, Levy P, Patel MM (2005) Procedural sedation and analgesia in the emergency department: what are the risks? Emerg Med Clin North Am 23: 551-572.
12. Robbertze R, Posner KL, Domino KB (2006) Closed claims

review of anesthesia for procedures outside the operating room. Curr Opin Anaesthesiol 19: 436-442.

13. Sacchetti A, Baren J, Carraccio C (2010) Total procedural requirements as indication for emergency department sedation. Pediatr Emerg Care 26: 209-211.

14. Statement on non-operating room anesthetizing location Edited by The American Society of Anesthesiologists. 2010.

15. Cheung KW, Watson ML, Field S, Campbell SG (2007) Aspiration pneumonitis requiring intubation after procedural sedation and analgesia: a case report. Ann Emerg Med 49: 462.

16. Sakai T, Planinsic RM, Quinlan JJ, Handley LJ, Kim TY, et al. (2006) The incidence and outcome of perioperative pulmonary aspiration in a university hospital: A 4-year retrospective analysis. Anesth Analg 103: 941-947.

17. Cepeda MS, Farrar JT, Baumgarten M, Boston R, Carr DB, et al. (2003) Side effects of opioids during short-term administration: effect of age, gender, and race. Clin Pharmacol Ther 74: 102-112.

18. Miner JR, Burton JH (2007) Clinical practice advisory: Emergency department procedural sedation with propofol. Ann Emerg Med 50: 182-187.

19. Green SM, Krauss B (2002) Pulmonary aspiration risk during emergency department procedural sedation--an examination of the role of fasting and sedation depth. Acad Emerg Med 9:35.

20. Green SM (2003) Fasting is a consideration--not a necessity--for emergency department procedural sedation and analgesia. Ann Emerg Med 42: 647-650.

21. Sandhar BK, Goresky GV, Maltby JR, Shaffer EA (1989) Effect of oral liquids and ranitidine on gastric fluid volume and pH in children undergoing outpatient surgery. Anesthesiology 71: 327-330.

22. Ljungqvist O, Søreide E (2003) Preoperative fasting. Br J Surg 90: 400-406.

23. Green SM, Roback MG, Miner JR (2007) Fasting and emergency department procedural sedation and analgesia: a consensus-based clinical practice advisory. Ann Emerg Med 49: 454.

24. Godwin SA, Burton JH, Gerardo CJ, Hatten BW, Mace SE, et al. (2014) Clinical policy: procedural sedation and analgesia in the emergency department. Ann Emerg Med 63: 247-258.

25. Bassett KE, Anderson JL, Pribble CG, Guenther E (2003) Propofol for procedural sedation in children in the emergency department. Ann Emerg Med 42: 773-782.

26. Sandhar BK, Goresky GV, Maltby JR, Shaffer EA (1989) Effect of oral liquids and ranitidine on gastric fluid volume and pH in children undergoing outpatient surgery. Anesthesiology 71: 327-330.

27. Harrington L (2006) Nurse-administered propofol sedation: a review of current evidence. Gastroenterol Nurs 29: 371-383.

28. Hogan K, Sacchetti A, Aman L, Opiela D (2006) The safety of single-physician procedural sedation in the emergency department. Emerg Med J 23: 922-923.

29. Maher EN, Hansen SF, Heine M, Meers H, Yaster M, et al. (2007) Knowledge of procedural sedation and analgesia of emergency medicine physicians. Pediatr Emerg Care 23: 869-876.

30. Deitch K, Chudnofsky CR, Dominici P (2007) The utility of supplemental oxygen during emergency department procedural sedation and analgesia with midazolam and fentanyl: a randomized, controlled trial. Ann Emerg Med 49: 1.

31. Miner JR, Biros MH, Heegaard W, Plummer D (2003) Bispectral electroencephalographic analysis of patients undergoing procedural sedation in the emergency department. Acad Emerg Med 10: 638.

32. Miner JR, Heegaard W, Plummer D (2002) End-tidal carbon dioxide monitoring during procedural sedation. Acad Emerg Med 9: 275.

33. McQuillen KK, Steele DW (2000) Capnography during sedation/analgesia in the pediatric emergency department. Pediatr Emerg Care 16: 401-404.

34. O'Sullivan I, Benger J (2003) Nitrous oxide in emergency medicine. Emerg Med J 20: 214-217.

35. Bahn EL, Holt KR (2005) Procedural sedation and analgesia: a review and new concepts. Emerg Med Clin North Am 23: 503-517.

36. Babl FE, Oakley E, Puspitadewi A, Sharwood LN (2008) Limited analgesic efficacy of nitrous oxide for painful procedures in children. Emerg Med J 25: 717-721.

37. Tobias JD, Leder M (2011) Procedural sedation: A review of sedative agents, monitoring, and management of complications. Saudi J Anaesth 5: 395-410.

38. Ben-Shlomo I, abd-el-Khalim H, Ezry J, Zohar S, Tverskoy M (1990) Midazolam acts synergistically with fentanyl for induction of anaesthesia. Br J Anaesth 64: 45-47.

39. Miner JR, Burton JH (2007) Clinical practice advisory: Emergency department procedural sedation with propofol. Ann Emerg Med 50: 182-187, 187.

40. Harris CE, Grounds RM, Murray AM, Lumley J, Royston D, et al. (1990) Propofol for long-term sedation in the intensive care unit. A comparison with papaveretum and midazolam. Anaesthesia 45: 366-372.

41. Beller JP, Pottecher T, Lugnier A, Mangin P, Otteni JC (1988) Prolonged sedation with propofol in ICU patients: Recovery and blood concentration changes during periodic interruption in infusion. Br J Anaesth. 61: 583–588.

42. Green SM, Krauss B (2003) Propofol in emergency medicine: pushing the sedation frontier. Ann Emerg Med 42: 792-797.

43. Black E, Campbell SG, Magee K, Zed PJ (2013) Propofol for procedural sedation in the emergency department: a qualitative systematic review. Ann Pharmacother 47: 856-868.

44. Newstead B, Bradburn S, Appelboam A, Reuben A, Harris A, et al. (2013) Propofol for adult procedural sedation in a UK emergency department: safety profile in 1008 cases. Br J Anaesth 111: 651-655.

45. Andolfatto G, Willman E (2011) A Prospective Case Series of Single-syringe Ketamine-Propofol (Ketofol) for Emergency Department Procedural Sedation and Analgesia in Adults. Acad Emerg Med 18: 237-245.

46. Green SM, Roback MG, Kennedy RM, Krauss B (2011)

Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med 57: 449-461.

47. Strayer RJ, Nelson LS (2008) Adverse events associated with ketamine for procedural sedation in adults. Am J Emerg Med 26: 985-1028.

48. Newton A, Fitton L (2008) Intravenous ketamine for adult procedural sedation in the emergency department: a prospective cohort study. Emerg Med J 25: 498-501.

49. Sener S, Eken C, Schultz CH, Serinken M, Ozsarac M (2011) Ketamine with and without midazolam for emergency department sedation in adults: a randomized controlled trial. Ann Emerg Med 57: 109-114.

50. Andolfatto G, Willman E (2011) A prospective case series of single-syringe ketamine-propofol (Ketofol) for emergency department procedural sedation and analgesia in adults. Acad Emerg Med 18: 237-245.

51. Miner JR, Moore JC, Austad EJ, Plummer D, Hubbard L, et al. (2014) Randomized, Double-Blinded, Clinical Trial of Propofol, 1:1 Propofol/Ketamine, and 4:1 Propofol/Ketamine for Deep Procedural Sedation in the Emergency Department. Ann Emerg Med 16.

52. Tobias JD (2012) Dexmedetomidine and ketamine: an effective alternative for procedural sedation? Pediatr Crit Care Med 13: 423-427.

53. Miner JR, Danahy M, Moch A, Biros M (2007) Randomized clinical trial of etomidate versus propofol for procedural sedation in the emergency department. Ann Emerg Med 49: 15-22.

54. Brown TB, Lovato LM, Parker D (2005) Procedural sedation in the acute care setting. Am Fam Physician 71: 85-90.

55. Keim SM, Erstad BL, Sakles JC, Davis V (2002) Etomidate for procedural sedation in the emergency department. Pharmacotherapy 22: 586-592.

56. Ruth WJ, Burton JH, Bock AJ (2001) Intravenous etomidate for procedural sedation in emergency department patients. Acad Emerg Med 8: 13-18.

57. Falk J, Zed PJ (2004) Etomidate for procedural sedation in the emergency department. Ann Pharmacother 38: 1272-1277.

58. Satoh M, Minami M (1995) Molecular pharmacology of the opioid receptors. Pharmacol Ther 68: 343-364.

59. Fahnenstich H, Steffan J, Kau N, Bartmann P (2000) Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. Crit Care Med 28: 836-839.

60. Müller P, Vogtmann C (2000) Three cases with different presentation of fentanyl-induced muscle rigidity--a rare problem in intensive care of neonates. Am J Perinatol 17: 23-26.

61. Becker DE (2012) Pharmacodynamic considerations for moderate and deep sedation. Anesth Prog 59: 28-42.

62. Miner JR, Gray R, Delavari P, Patel S, Patel R, et al. (2011) Alfentanil for procedural sedation in the emergency department. Ann Emerg Med 57: 117-121.

63. Ab-Rahman NH, Hashim A (2008) A randomized controlled trial on procedural sedation among adult patients in emergency departments: comparing fentanyl with midazolam versus fentanyl with propofol. Ann Emerg Med 51: 479.

64. Trissel LA, Gilbert DL, Martinez JF (1997) Compatibility of propofol injectable emulsion with selected drugs during simulated Y-site administration. Am J Health Syst Pharm 54: 1287-1292.

65. Aouad MT, Moussa AR, Dagher CM, Muwakkit SA, Jabbour-Khoury SI, et al. (2008) Addition of ketamine to propofol for initiation of procedural anesthesia in children reduces propofol consumption and preserves hemodynamic stability. Acta Anaesthesiol Scand 52: 561-565.

66. Badrinath S, Avramov MN, Shadrick M, Witt TR, Ivankovich AD (2000) The use of a ketamine-propofol combination during monitored anesthesia care. Anesth Analg 90: 858-862.

67. Daabiss M, Elsherbiny M and Alotibi R (2009) Assessment of different concentration of Ketofol in procedural operation. BJMP 2: 27-31.

68. Coulter FL, Hannam JA, Anderson BJ (2014) Ketofol dosing simulations for procedural sedation. Pediatr Emerg Care 30: 621-630.

69. Loh G, Dalen D (2007) Low-dose ketamine in addition to propofol for procedural sedation and analgesia in the emergency department. Ann Pharmacother 41: 485-492.

70. David H, Shipp J (2011) A randomized controlled trial of ketamine/propofol versus propofol alone for emergency department procedural sedation. Ann Emerg Med 57: 435.

71. Phillips W, Anderson A, Rosengreen M, Johnson J, Halpin J (2010) Propofol versus propofol/ketamine for brief painful procedures in the emergency department: clinical and bispectral index scale comparison. J Pain Palliat Care Pharmacother 24: 349.

72. Gerlach AT, Dasta JF (2007) Dexmedetomidine: an updated review. Ann Pharmacother 41: 245-252.

73. Devasya A, Sarpangala M (2015) Dexmedetomidine: Dexmedetomidine: A Review of a Newer Sedative in Dentistry. Journal of Clinical Pediatric Dentistry 39: 401-409.

74. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD (2000) The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 93: 382-394.

75. Dyck JB, Maze M, Haack C, Azarnoff DL, Vuorilehto L, et al. (1993) Computer-controlled infusion of intravenous dexmedetomidine hydrochloride in adult human volunteers. Anesthesiology 78: 821-828.

76. Ustün Y, Gündüz M, ErdoÄŸan O, Benlidayi ME (2006) Dexmedetomidine versus midazolam in outpatient third molar surgery. J Oral Maxillofac Surg 64: 1353-1358.

77. Cheung CW, Ying CL, Chiu WK, Wong GT, Ng KF, et al. (2007) A comparison of dexmedetomidine and midazolam for sedation in third molar surgery. Anaesthesia 62: 1132-1138.

78. Taniyama K, Oda H, Okawa K, Himeno K, Shikanai K, et al. (2009) Psychosedation with dexmedetomidine hydrochloride during minor oral surgery. Anesth Prog 56: 75-80.

79. Makary L, Vornik V, Finn R, Lenkovsky F, McClelland AL, et al. (2010) Prolonged recovery associated with dexmedetomidine when used as a sole sedative agent in office-based oral and maxillofacial surgery procedures. J Oral Maxillofac Surg 68: 386-391.

80. Munro HM, Tirotta CF, Felix DE, Lagueruela RG, Madril DR, et al. (2007) Initial experience with dexmedetomidine for diagnostic and interventional cardiac catheterization in children. Paediatr Anaesth 17: 109-112.

81. Young ET (2005) Dexmedetomidine sedation in a pediatric cardiac patient scheduled for MRI. Can J Anaesth 52: 730-732.

82. Heard CM, Joshi P, Johnson K (2007) Dexmedetomidine for pediatric MRI sedation: a review of a series of cases. Paediatr Anaesth 17: 888-892.

83. Jalowiecki P, Rudner R, Gonciarz M, Kawecki P, Petelenz M, et al. (2005) Sole use of dexmedetomidine has limited utility for conscious sedation during outpatient colonoscopy. Anesthesiology 103: 269-273.

84. Alhashemi JA (2006) Dexmedetomidine vs midazolam for monitored anaesthesia care during cataract surgery. Br J Anaesth 96: 722-726.

85. Levänen J, Mäkelä ML, Scheinin H (1995) Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium. Anesthesiology 82: 1117-1125.

86. Tobias JD1 (2012) Dexmedetomidine and ketamine: an effective alternative for procedural sedation? Pediatr Crit Care Med 13: 423-427.

87. Mahmoud M, Tyler T, Sadhasivam S (2008) Dexmedetomidine and ketamine for large anterior mediastinal mass biopsy. Paediatr Anaesth 18: 1011-1013.

88. Luscri N, Tobias JD (2006) Monitored anesthesia care with a combination of ketamine and dexmedetomidine during magnetic resonance imaging in three children with trisomy 21 and obstructive sleep apnea. Pediatr Anesth 16: 782–786.

89. Nelson TM, Xu Z (2015) Pediatric dental sedation: challenges and opportunities. Clin Cosmet Investig Dent 7: 97-106.

90. Bhoi S, Chandra A, Galwankar S (2010) Ultrasound-guided nerve blocks in the emergency department. J Emerg Trauma Shock 3: 82-88.

91. Fitch RW, Kuhn JE (2008) Intraarticular lidocaine versus intravenous procedural sedation with narcotics and benzodiazepines for reduction of the dislocated shoulder: a systematic review. Acad Emerg Med 15: 703-708.

92. Gazal G, Fareed WM, Zafar MS and Al-Samadani K (2016) Pain and anxiety management for pediatric dental procedures using various combinations of sedative drugs: A review. Saudi Pharmaceutical 24: 379–385.

93. Krauss B, Green SM (2006) Procedural sedation and analgesia in children. Lancet 367: 766-780.

94. Kost S, Roy A (2010) Procedural Sedation and Analgesia in the Pediatric Emergency Department: A Review of Sedative Pharmacology. Clinical Pediatric Emergency Medicine 11: 233-243.

95. McMorrow SP, Abramo TJ (2012) Dexmedetomidine sedation: uses in pediatric procedural sedation outside the operating room. Pediatr Emerg Care 28: 292-296.

96. Neuman G, Koren G (2013) Safety of procedural sedation in pregnancy. J Obstet Gynaecol Can 35: 168-173.

97. Royal College of Anaesthetists and College of Emergency Medicine (2012) Safe sedation of adults in the emergency department.

98. Newman DH, Azer MM, Pitetti RD, Singh S (2003) When is a patient safe for discharge after procedural sedation? The timing of adverse effect events in 1367 pediatric procedural sedations. Ann Emerg Med 42: 627-635.