OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article **Dentistry**

A Narrative Review of Sedatives used in Critically Ill Patients in ICU

Siraj DAA Khan[1*], Fatimah Mesfer Alshahrani[2], Noura Faisal Alkhalifa[2]

[1]Faculty of Dentistry, Najran University, Saudi Arabia
[2]College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, Saudi Arabia

DOI: 10.36348/sjmps.2023.v09i07.015 | **Received:** 12.06.2023 | **Accepted:** 17.07.2023 | **Published:** 26.07.2023

***Corresponding author:** Siraj DAA Khan
Faculty of Dentistry, Najran University, Saudi Arabia

Abstract

Patients in the intensive care unit are treated with many interventions to keep them on rest. A number of sedatives are used in ICU for this purpose. The main aim of sedation is to control pain. Benzodiazepines are commonly used as sedative agents and adjuvants. Many adverse effects such as CNS depression and respiratory depression have been associated with the use of these drugs. Propofol has satisfactory sedative effects. It can also be combined with other medicines to achieve the required results. Slow heart rate (Bradycardia), low blood pressure (Hypotension), and hyperlipidemia are common effects after the infusion of Propofol. Dexmedetomidine (DEX) is a suitable drug for sedation in cardiac patients. Less respiratory depression and analgesia are advantages of Dexmedetomidine over benzodiazepines. It can be concluded that the dose of sedatives must keep to a minimum effective level for having safe results for the patient and to make the patient mobilized at the earliest when possible.

Keywords: CNS, depression, respiratory, bradycardia, dexmedetomidine.

INTRODUCTION

Many interventions are used for patients in ICU who are critically ill, like passing endotracheal tubes and putting them on mechanical ventilation which may be very distressing. The most common distressing factor is pain which is in memory of patients who had a stay in the ICU [1]. Different catheters used for IV lines and endotracheal tubes may be removed by an agitated patient which can make monitoring and administration of life-sustaining medicines difficult. To overcome this situation, sedatives are the most common medicines used in ICU. To reduce the pain and provide adequate analgesia are important in ICU. High expenditures of energy and immunomodulation are short-term unwanted results of untreated pain in the ICU. Post-traumatic stress disorder is a long-term side effect of untreated pain [2, 3]. Assessment of pain in critically ill patients is a difficult task. The standard for pain assessment is reporting by the patient but critically ill patients may not be so interactive to give a good response. Other physiological indicators like blood pressure and heart rate have a poor correlation with valid measures of pain but other scales like the Behavioral Pain Scale and the CriticalCare Pain Observation Tool give good and repeatable assessments and are the best available methods which are currently used for assessment in critically ill patients [4-6].

SEDATION IN ICU

Practices of sedation in intensive care unit (ICU) have changed dramatically in the last 20 years. In history sedation was used in patients to keep them on rest [7, 8]. Recent strong pieces of evidence show that this practice is associated with dangers and has unwanted and poor outcomes [9]. Practice of the current era is to use a minimum dose of sedation and to wake patients up daily to make them comfortable [10]. In a trial study a comparison was made between routine daily interruption of sedative infusion and discretionary interruption of sedative infusion by the treating doctor and the result was that the patients who received routine interruptions in sedation infusion required overall less sedation and they spent fewer days on ventilators in ICU [11]. A larger trial was conducted where routine interruptions of sedative infusions were combined with spontaneous daily breathing trials. Low dose of benzodiazepine sedatives, reduced time spent on a mechanical ventilator and reduced stay in ICU, and significantly increased survival rate was associated with daily interruption of sedative infusion. Results showed that interruption of sedation and minimal dose of sedatives provide desired clinical outcomes [12].

Table 1: Common sedative used in ICU and their effects

Drug Name	Pharmacokinetic of drug	Mechanism of Action	Effects of Drug
Benzodiazepines	Accumulation of metabolite and prolonged infusion; metabolized by hepatic oxidation, excretion of the active metabolite	$GABA_A$ agonist	high risk of delirium and tolerance as compared to some other sedatives
Propofol	Metabolized by hepatic hydroxylation and glucuronidation	Glutamate and cannabinoid receptors, $GABA_A$ agonist	hypotension or bradycardia; propofol infusion syndrome (cardiac arrest, arrhythmia and lactic acidosis), prolonged infusion rates, pancreatitis, hypertriglyceridemia;
Dexmedetomidine	It does not accumulate, metabolized by hepatic oxidation and glucuronidation	α2-Agonist	Dry mouth, bradycardia, Transient hypertension, then hypotension, nausea

Furthermore, depth of sedation is also associated with the duration of the patient on mechanical ventilation, mortality rate in the hospital, and death rate within 180 days of ICU stay. Use of lighter sedatives resulted in fewer days on a ventilator as well as in ICU in another controlled randomized trial. In a comparison between lighter sedation and deep sedation, the lighter sedation resulted in fewer short-term adverse effects and improvements in long-term psychiatric outcomes [13-15]. Lighter sedation in critically ill adult patients in ICU resulted in shorter extubation time and reduced chances for tracheostomy as summarized in The Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU, known as PADIS guidelines. Surveys show that despite close monitoring in ICUs, the depth of sedation can frequently go unmonitored. This finding may be surprising and unacceptable because studies have shown that good monitoring of sedation can have positive outcomes in critically ill patients in ICUs [16, 17].

BENZODIAZEPINES

Most benzodiazepines are used as sedative agents and adjuvants [18]. Benzodiazepines can be classified according to various criteria like elimination half-life, duration of action, and chemical structure. A short-acting benzodiazepine is described as having a half-life of less than 24 hours and a long-acting benzodiazepine is described as having a half-life of more than 24 hours. Benzodiazepines have many benefits for persons with severe mental disorders, but they may also lead to or exacerbate substance abuse [19, 20]. A common similarity in the structure of benzodiazepines is the fusion of benzene ring with the diazepine ring. In some benzodiazepines additional cyclic units are found like alprazolam has a triazole ring, midazolam has an imidazole ring and cloxazolam has an oxazole ring [19].

EFFECTS OF BENZODIAZEPINES

They are not used primarily as inducing agents because of their high variability in patient drug response, less potency, slow onset of action, and negative effects for a long time. CNS depression, Respiratory depression, muscle relaxation, and anticonvulsant effects are unwanted side effects of benzodiazepines. Muscle relaxation and anticonvulsant properties may be beneficial for patients undergoing general anesthesia. In the mechanism of action of these drugs, their interactions with chloride channels and GABA can lead to the inhibition of polysynaptic pathways. Central nervous system has an inhibitory neurotransmitter named Gamma amino butyric acid (GABA). It acts on subtype receptors A, B, and C. Benzodiazepines act on the GABA-A receptors to produce their effects [21-23]. The GABA-A is a chloride- selective ion channel that is ligand-gated. 5 subunits including 2 alpha 2 beta and 1 gamma subunit are found in it. A pocket formed by alpha and gamma subunits is the site of action of benzodiazepines where they act as positive allosteric modulators. There is a single benzodiazepine binding site as compared to two GABA molecule binding sites on the GABA-A receptor [24]. A conformational change takes place in chloride channels when benzodiazepine binds to the GABA-A receptor and leads to hyperpolarization. This hyperpolarization leads to inhibition of the central nervous system [25].

PROPOFOL

Imperial Chemical Industries Limited (London, UK) developed a potent intravenous sedative, Propofol (2,6- diisopropylphenol) and it was patented by John (Iain) Glen and Roger James in 1977. It was launched commercially in Europe in 1986 and in the US in 1989. Propofol (2,6-diisopropyl phenol) is a phenolic derivative with satisfactory sedative, hypnotic, antiemetic and amnesic properties and also with minimal analgesic action. It is a highly lipophilic agent that can easily cross the blood-brain barrier and as a result, has a rapid onset of action (< 1 min).It is a c-aminobutyric acid (GABA) receptor agonist like most sedatives with favorable pharmacokinetic (PK) and pharmacodynamic (PD) profiles. Therefore it is the

most commonly used intravenous sedative for the last three decades [26-29]. Its efficacy and use in critically ill patients in the intensive care unit (ICU) are proven for sedation. Propofol can also be combined with other sedative agents to achieve a synergistic sedative effect. Propofol monotherapy and propofol combined therapy was shown to have comparable efficacy in a recent meta-analysis of 22 RCTs that involved 2250 patients [30-31].

EFFECTS OF PROPOFOL

Its adverse effects are well documented with pain at the site of injection being the most common adverse effect. Slow heart rate (Bradycardia), low blood pressure (Hypotension) and metabolic effects like hyperlipidemia after infusion of lipid formulation are other common adverse effects [32]. PAD (The Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult ICU Patients) was published in 2013 which reported that patients had shorter time on ventilation who received propofol as compared to the patients who received intermittent lorazepam. PADIS (The Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU) were published in 2018. PADIS suggested light sedation with the help of propofol in cardiac patients instead of benzodiazepines. Propofol has not been proven to reduce mortality as compared to benzodiazepines but it helps in reducing the stay in the intensive care unit ICU [33].

DEXMEDETOMIDINE

For a patient with cardiac surgery in the intensive care unit ICU, Dexmedetomidine (DEX) is a suitable sedative that is an alpha-2 adrenergic agonist.47% absolute risk reduction of delirium after a loading dose of 0.4 mg kg^{-1} of DEX followed by a continuous infusion of suitable dose as compared with propofol sedation was shown in a study. It was proved by MENDS **(**Maximizing the Efficacy of Sedation and Reducing Neurological Dysfunction) that the frequency of coma and delirium was less in patients who received DEX and they were within 1 point of the target, The Richmond Agitation Sedation Scale (RASS) as compared to lorazepam [34].

EFFECTS OF DEXMEDETOMIDINE

The chances of main side effects including bradycardia and hypotension after using a low dose rate of DEX would theoretically be reduced. 375 patients from 68 centers in 5 different countries who were mechanically ventilated were studied for efficacy and safety with prolonged sedation with dexmedetomidine versus midazolam. The benefits of dexmedetomidine as compared to midazolam were low prevalence of delirium during the stay in ICU, shorter time for extubation, and lower chances of cardiac side effects like tachycardia and hypotension but no difference in time spent within Richmond Agitation-Sedation Scale goal was observed. Less respiratory depression and analgesia are other advantages of Dexmedetomidine over benzodiazepines and different type of qualitative sedation is provided by DEX in which patients are more interactive and can communicate more effectively about their needs [35, 36].

OTHER SEDATIVES

Earlier fluorinated ethers were used for the induction and maintenance of general anesthesia. Their use for sedation in critically ill patients in ICU on mechanical ventilation has recently come to light. Recent studies have been made about Remifentanil for its safety and efficacy as a sedative agent, especially when used in combination with other benzodiazepines and propofol [37].

Remifentanil has been investigated as a sedative agent in ICUs predominantly among surgical patients. Although remifentanil has been associated with a reduced duration of mechanical ventilation and ICU stay in these small trials, it has not yet been evaluated in a large, heterogeneous population of critically ill patients and is currently not a common choice in most ICUs [38, 39].

CONCLUSION

Management of sedation and delirium can have positive and good effects on the outcomes of critically ill patients who are mechanically ventilated in ICUs as suggested by studies. For achieving best outcomes according to currently available data the use of such protocol is required in which depth of sedation and presence of delirium and pain are continuously monitored and pain is treated effectively and promptly. The dose of sedatives is kept to a minimum effective level for having safe results for the patient, to keep the patient comfortable, and to make the patient mobilized at the earliest when possible.

REFERENCES

1. Stein-Parbury, J., & McKinley, S. (2000). Patients' experiences of being in an intensive care unit: a select literature review. *Am J Crit Care*, *9*, 20-7.
2. Page, G. G., Blakely, W. P., & Ben-Eliyahu, S. (20010. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. *Pain*, *90*, 191-9.
3. Myhren, H., Ekeberg, O., Toien, K., Karlsson, S., & Stokland, O. (2010). Posttraumatic stress, anxiety and depression symptoms in patients during the first year post intensive care unit discharge. *Crit Care*, *14*(1), R14.
4. Gélinas, C., Tousignant-Laflamme, Y., Tanguay, A., & Bourgault, P. (2011). Exploring the validity of the bispectral index, the Critical- Care Pain Observation Tool and vital signs for the detection of pain in sedated and mechanically ventilated

critically ill adults: a pilot study. *Intensive Crit Care Nurs*, *27*, 46-52.

5. Payen, J. F., Bru, O., Bosson, J. L., Lagrasta, A., Novel, E., Deschaux, I., ... & Jacquot, C. (2001). Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Critical care medicine*, *29*(12), 2258-2263.
6. Gélinas, C., Fillion, L., Puntillo, K. A., Viens, C., & Fortier, M. (2006). Validation of the critical-capain observation tool in adult patients. *Am J Crit Care*, *15*, 420-7.
7. Barr, J., Fraser, G. L., Puntillo, K., Ely, E. W., Gélinas, C., Dasta, J. F., ... & Jaeschke, R. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical care medicine*, *41*(1), 263-306.
8. Shapiro, B. A., Warren, J., Egol, A. B., Greenbaum, D. M., Jacobi, J., Nasraway, S. A., ... & Stone, J. R. (1995). Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. *Critical care medicine*, *23*(9), 1596-1600.
9. Needham, D. M., Davidson, J., Cohen, H., Hopkins, R. O., Weinert, C., Wunsch, H., ... & Harvey, M. A. (2012). Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Critical care medicine*, *40*(2), 502-509.
10. Devlin, J. W., Skrobik, Y., Gélinas, C., Needham, D. M., Slooter, A. J., Pandharipande, P. P., ... & Alhazzani, W. (2018). Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Critical care medicine*, *46*(9), e825-e873.
11. Kress, J. P., Pohlman, A. S., O'Connor, M. F., & Hall, J. B. (2000). Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New England Journal of Medicine*, *342*(20), 1471-1477.
12. Girard, T. D., Kress, J. P., Fuchs, B. D., Thomason, J. W., Schweickert, W. D., Pun, B. T., ... & Ely, E. W. (2008). Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *The Lancet*, *371*(9607), 126-134.
13. Shehabi, Y., Bellomo, R., Reade, M. C., Bailey, M., Bass, F., Howe, B., ... & Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the ANZICS Clinical Trials Group. (2012). Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *American journal of respiratory and critical care medicine*, *186*(8), 724-731.
14. Treggiari, M. M., Romand, J. A., & Yanez, N. D. (2009). Randomized trial of light versus deep sedation on mental health after critical illness. *Crit Care Med*, *37*, 2527-34.
15. Strøm, T., Stylsvig, M., & Toft, P. (2011). Long-term psychological effects of a no-sedation protocol in critically ill patients. *Critical Care*, *15*, 1-8.
16. Soliman, H. M., Mélot, C., & Vincent, J. L. (2001). Sedative and analgesic practice in the intensive care unit: the results of a European survey. *British journal of anaesthesia*, *87*(2), 186-192.
17. De Jonghe, B., Bastuji-Garin, S., Fangio, P., Lacherade, J. C., Jabot, J., Appéré-De-Vecchi, C., ... & Outin, H. (2005). Sedation algorithm in critically ill patients without acute brain injury. *Critical care medicine*, *33*(1), 120-127.
18. Cornett, E. M., Novitch, M. B., Brunk, A. J., Davidson, K. S., Menard, B. L., Urman, R. D., & Kaye, A. D. (2018). New benzodiazepines for sedation. *Best Practice & Research Clinical Anaesthesiology*, *32*(2), 149-164.
19. Manchester, K. R., Lomas, E. C., Waters, L., Dempsey, F. C., & Maskell, P. D. (2018). The emergence of new psychoactive substance (NPS) benzodiazepines: a review. *Drug testing and analysis*, *10*(1), 37-53. doi:10.1002/dta.2211.
20. Clark, R. E., Xie, H., & Brunette, M. F. (2004). Benzodiazepine prescription practices and substance abuse in persons with severe mental illness. *Journal of Clinical Psychiatry*, *65*(2), 151-155.
21. Kanto, J., & Klotz, U. (1982). Intravenous benzodiazepines as anaesthetic agents: pharmacokinetics and clinical consequences. *Acta Anaesthesiologica Scandinavica*, *26*(6), 554-569.
22. Hirschtritt, M. E., Delucchi, K. L., & Olfson, M. (2018). Outpatient, combined use of opioid and benzodiazepine medications in the United States, 1993–2014. *Preventive medicine reports*, *9*, 49-54. doi:10.1016/j.pmedr.2017.12.010.
23. Griffin, C. E., Kaye, A. M., Bueno, F. R., & Kaye, A. D. (2013). Benzodiazepine pharmacology and central nervous system–mediated effects. *Ochsner Journal*, *13*(2), 214-223.
24. Manchikanti, L., Christo, P. J., Trescot, A., Falco, F. J. E., & American Society of Interventional Pain Physicians. (Pain medicine & interventional pain management: a comprehensive review: clinical aspects.
25. Kelly, M. D., Smith, A., Banks, G., Wingrove, P., Whiting, P. W., Atack, J., ... & Maubach, K. A. (2002). Role of the histidine residue at position 105 in the human α5 containing GABAA receptor on the affinity and efficacy of benzodiazepine site ligands. *British journal of pharmacology*, *135*(1), 248-256. doi:10.1038/sj.bjp.0704459.
26. Glen, J. B., & James, R. (1977). 2,6-Diisopropylphenol as an anaesthetic agent. London: United States Patent and Trademark Office; p. 1-10.

27. Thompson, K. A., & Goodale, D. B. (2000). The recent development of propofol (DIPRIVAN). *Intensive Care Med*, *26*(Suppl 4), S400–4.
28. Ferreira, A. O. (2015). Sedation in gastrointestinal endoscopy: Where are we at in 2014? World J Gastrointest Endosc, 7, 102.
29. Schuttler, J., & Schwilden, H. (editors). (2008). Modern anesthetics (handbook of experimental pharmacology), vol. 182. Heidelberg: Springer.
30. Liu, H., Ji, F., Peng, K., Applegate, R. L., & Fleming, N. (2017). Sedation after cardiac surgery: is one drug better than another? *Anesth Analg*, *124*, 1061–70.
31. Yoon, S. W., Choi, G. J., Lee, O. H., Yoon, I. J., Kang, H., Baek, C. W., ... & Woo, Y. C. (2018). Comparison of propofol monotherapy and propofol combination therapy for sedation during gastrointestinal endoscopy: A systematic review and meta-analysis. *Digestive Endoscopy*, *30*(5), 580-591. [Epub ahead of print].
32. Marik, P. E. (2004). Propofol: therapeutic indications and side-effects. *Curr Pharm Des*, *10*, 3639–49.
33. Ho, K. M., & Ng, J. Y. (2008). The use of propofol for medium and long-term sedation in critically ill adult patients: a meta-analysis. *Intensive care medicine*, *34*, 1969-1979.
34. Maldonado, J. R., Wysong, A., Van Der Starre, P. J., Block, T., Miller, C., & Reitz, B. A. (2009). Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics*, *50*(3), 206-217.
35. Riker, R. R., Shehabi, Y., Bokesch, P. M., Ceraso, D., Wisemandle, W., Koura, F., ... & Rocha, M. G. (2009). Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *Jama*, *301*(5), 489-499.
36. Jakob, S. M., Ruokonen, E., Grounds, R. M., Sarapohja, T., Garratt, C., Pocock, S. J., ... & Dexmedetomidine for Long-Term Sedation Investigators. (2012). Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *Jama*, *307*(11), 1151-1160.
37. Sackey, P. V., Martling, C. R., Granath, F., & Radell, P. J. (2004). Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. *Critical care medicine*, *32*(11), 2241-2246.
38. Muellejans, B., Matthey, T., Scholpp, J., & Schill, M. (2006). Sedation in the intensive care unit with remifentanil/propofol versus midazolam/fentanyl: a randomised, open-label, pharmacoeconomic trial. *Critical Care*, *10*(3), 1-9.
39. Spies, C., MacGuill, M., Heymann, A., Ganea, C., Krahne, D., Assman, A., ... & Martin, J. (2011). A prospective, randomized, double-blind, multicenter study comparing remifentanil with fentanyl in mechanically ventilated patients. *Intensive care medicine*, *37*, 469-476.