REVIEW ARTICLE

Advantages of dexmedetomidine in traumatic brain injury - a review

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ABSTRACT

Patients with traumatic brain injury (TBI) require mechanical ventilation for airway protection, to reduce work of breathing, to reduce cerebral metabolic rate and to optimize intracerebral hemodynamics. Drugs like narcotics, benzodiazepines, propofol and alpha-2 agonists with or without non-depolarizing muscle relaxants are used to facilitate mechanical ventilation. We reviewed literature on search engines PubMed and Medline to determine the efficacy and feasibility of dexmedetomidine as the sole sedative agent in patients with TBI in terms of maintenance of hemodynamics, ease of neurological assessment with ongoing sedation and long term neurological outcome.

Key words: Dexmedetomidine; Brain injuries; Propofol; Benzodiazepines; Narcotics

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INTRODUCTION

Clinicians use sedatives in mechanically ventilated patients with TBI to facilitate mechanical ventilation, to reduce intracranial pressure (ICP) , to decrease cerebral metabolic rate ($CMRO_2$) and to terminate seizures. The idea is to prevent further damage by improving oxygenation, to decrease work of breathing and to decrease sympathetic drive. Anesthesia and critical care armamentarium has several drugs that alone or in combination can be used for serving this purpose. Several agents have additional beneficial effects like analgesic and anti-convulsive properties which can be useful in such patients. The characteristics of an ideal agent in neurocritical care (especially in TBI) are: it should be short acting, have no respiratory depression, shouldn't have active metabolites, should not cause hemodynamic compromise, desirable to have properties, should be able to reduce $CMRO_2$ and should have analgesic properties.

Dexmedetomidine is a centrally acting α2 agonist approved by United States FDA for ICU sedation upto 24 hours. However, the last decade has seen extensive use of dexmedetomidine in every situation in intensive care and in all specialties by anesthesiologists as an adjunct to general or regional anesthesia. It provides excellent sedation without respiratory depression, has no residual metabolites, provides analgesia, has sympatholytic properties and need not be stopped during weaning the patient from mechanical ventilation or for neurological assessment.[1-3] The literature describes favorable effects on cerebral hemodynamics. However, it shows no anticonvulsive effects of this drug.

METHODOLOGY

We searched PubMed and Medline using keywords 'dexmedetomidine' and 'brain injuries'. We also searched 'propofol', 'benzodiazepines' and 'narcotics' with 'brain injuries' separately. We reviewed the literature available on the use of dexmedetomidine in experimental animals and humans with traumatic brain injury to ascertain its efficacy for short as well as long term use. We also reviewed in brief the literature available on use of propofol in

TBI and the effects of routinely used anesthetic

agents on cerebral hemodynamics and neurological outcome in managing patients with TBI in operating room and ICU.

REVIEW

Clinicians use propofol more commonly as the sedative for patients with TBI due to its extensively described neuroprotective effects.[4] Many use benzodiazepines or narcotics alone or in combination for the same purpose. Due to prolonged sedative effects, barbiturates are not very popular now. Inhalational anesthetics are known to have neuroprotective abilities but the use is restricted in operating rooms and is rarely continued in the ICU. Roberts et al reviewed 13 randomised controlled trials involving 380 patients.

They found no convincing evidence of efficacy of any one sedative agent in terms of patient outcomes, ICP or cerebral perfusion pressure (CPP) in critically ill patients with TBI. They however felt that high bolus doses of opioids had deleterious effects on ICP and CPP.[5]Urwin et al felt that careful titration of dose, combination of agents and understanding the pharmacology of agents can help in proper utilization of sedatives.[6] However combination of agents can potentiate sedative effects and can make neurological assessment difficult and can also cause hemodynamic issues if not combined judiciously. Use of nondepolarizing muscle relaxants(NDMR) along with sedatives can further complicate neurological assessment.

ANESTHETIC AGENTS IN TBI

Propofol

Adembri et al reviewed neuroprotective effects of propofol in acute cerebral injury and suggested that propofol should not be considered as a clinical neuroprotectant but should be used as a part of multimodal neuroprotection like maintenance of CPP, temperature and seizure control, prevention of infections and glycemic control.[7] Kotani et al described how propofol functions as a neuroprotective agent by decreasing CBF and ICP by activating GABA- A receptors, inhibiting NMDA receptors and modulating calcium influx. The EDTA component in propofol also has antibacterial and antifungal properties.[8]

Johnston et al felt that although by using propofol infusion in TBI preserves the flow-metabolism coupling and increases EEG burst suppression ratio in patients with TBI, it doesn't reduce the level of regional ischemic burden.[9] Tanguy et al compared effects of propofol and midazolam on cerebral biomarkers in acute phase of TBI by randomizing 30 patients. With a cerebral microdialysis catheter they measured lactate:pyruvate (L:P) ratio, glutamate, glycerol and glucose for 72 hrs. They observed no difference in L:P ratio and glutamate levels and concluded that there is no difference between propofol and midazolam sedation as far as cerebral metabolic profile in TBI is concerned.[10]Ghori et al randomly assigned 28 patients with TBI to receive propofol and midazolam as sedatives to collect blood samples for 5 days for estimating S100beta and nitric oxide (NO) concentration. They assessed neurological outcome after 3 months and found that increased serum S100beta concentration was related to a poor neurological outcome and not the type of sedation that was used.[11]

Propofol infusion syndrome:

Propofol offers excellent quality of sedation and weaning from the infusion is easy. However it doesn't have analgesic properties. Also, there are limitations of using propofol infusion for a longer duration. Propofol infusion syndrome is observed in some patients who receive propofol infusion for more than 48 hours in doses more than 4 mg/kg/hr. The syndrome presents as metabolic acidosis (base excess >10 mmol/L), rhabdomyolysis, hyperlipidemia and fatty liver. Acute refractory bradycardia leading to a systole is usually the terminal event. Predisposing factors for this syndrome are severe critical illness, catecholamine and glucocorticoid use, decreased carbohydrate intake, subclinical mitochondrial disease. Hemodialysis or hemoperfusion with aggressive cardiovascular support is required to avoid mortality.[12-16]

Other anesthetic agents

Schifilliti et al conducted an extensive literature search of > 30 years by reviewing more than 600 articles and suggested that anesthetic agents like barbiturates, propofol, xenon and all volatile agents exerts neuroprotective effects that protects cerebral tissue from apoptosis, degeneration, inflammation and energy failure due to neurodegenerative diseases, ischemia, stroke or trauma. At the same time they also mentioned that all anesthetics were associated with dose and exposure dependent neurodegenerative effects in developing animal brain.[17] But Head et al felt that the neuroprotective effects of anesthetics are not helpful in severe injuries[18] Koerner et al reviewed the beneficial effects of anesthetic agents especially isoflurane and xenon and mentioned that the neuroprotection could be

due to suppression of excitatory neurotransmission and potentiation of inhibitory activity.[19] Statler et al compared 7 anesthetic agents in adult male rats who were subjected to experimental TBI. The agents were: diazepam, fentanyl, isoflurane, ketamine, morphine, pentobarbital and propofol.

They found that rats treated with isoflurane had best cognitive recovery. However, using isoflurane in ICU on a mechanically ventilated patient will require anesthesia work station.[20] Taufeeq et al described the neuroprotective effects of Isoflurane.[21] Flower et al described in detail the various categories of sedatives used and the advantages / disadvantages in TBI. The sedatives described by them were: propofol, benzodiazepines, narcotics, barbiturates, etomidate, ketamine and dexmedetomidine.[22]

Etomidate never became popular as a sedative in patients with TBI, possibly due to its adrenal suppression which is possible even with a single dose.[23] Chang et al described the neuroprotective effects of ketamine in patients with TBI and also stated that ketamine doesn't actually cause an increase in ICP when used for induction, maintenance sedation in ICU.[24] However ketamine sedation is usually not practiced these days due to availability of better drugs. The infusion of ketamine leads to secretions, delirium, and difficulty in assessing neurological status as benzodiazepines are usually used to counteract delirium. Rhoney et al described the effect of sedatives used in ICU on cerebral physiology.[25] Roberts et al reviewed the efficacy of barbiturates in TBI and found that there is no evidence of barbiturate therapy in TBI.[26] On the contrary, the hypotension produced during the ongoing infusion can be disastrous for maintaining optimum CPP. Weaning patients from ventilator also gets difficult due to barbiturate infusion.

DEXMEDETOMIDINE IN TBI

The favourable properties of dexmedetomidine like no respiratory depression, ease of arousability, analgesic properties , short acting effects and sympatholytic effect suits as an ideal sedative agent for patients with TBI.[27] Lots of articles are published describing the efficacy and safety of dexmedetomidine in patients with head injury.

Hao et al enrolled 90 patients with moderate and severe head injury and compared effects of dexmedetomidine and propofol on quality of sedation and endorphins in TBI and concluded that sedation efficacy of dexmedetomidine was superior to propofol in terms of hemodynamic control and decreased stress response. They also found that plasma endorphin level was elevated in early phase of brain injury by dexmedetomidine which was considered as its positive role in regulation of early stress.[28]

James et al conducted a pilot study using a randomized, crossover, unblended clinical trial and included patients with severe brain injury of GCS < 8 (TBI, subarachnoid hemorrhage, intracerebral hemorrhage) with multimodal monitoring like ICP, brain temperature, oximetry and microdialysis. Patients received an infusion of either propofol or dexmedetomidine for 6 hrs and then a crossover for subsequent 6 hrs. They concluded that both dexmedetomidine and propofol are equally effective and neither is associated with adverse hemodynamic effects.[29] Schoeler et al subjected organotypic hippocampal slice cultures to focal trauma, exposed it to varying concentration of dexmedetomidine and assessed cell injury after 72 hours. They found that dexmedetomidine showed protective effect on the hippocampal cells.[30] Nakano et al studied effects of dexmedetomidine on cerebral blood flow and mean arterial pressure in 42 rats in doses ranging from 1 to 10 ug/kg/min.

These rats were subjected to transient middle cerebral artery occlusion. Five days after the occlusion, the infarct volume was measured which was found to be more in rats which received higher doses of dexmedetomidine. They concluded that high dose is associated with cerebral hypoperfusion which can be avoided by either reducing or avoiding the loading dose of dexmedetomidine.[31] Benggon et al studied the efficacy of dexmedetomidine on reducing brain edema and improvement in neurological outcomes after inducing surgical brain injury in 63 rats receiving the drug. They found that there is no role of dexmedetomidine in this

scenario.[32]

Catecholamine surge and its effects in TBI:

There is an increase in intracellular calcium which leads to excessive excitability due to increased sensitivity of pyramidal neurons to glutamate. There is direct toxicity of neuronal tissue due to increased catecholamines and increase in free radical release. There is decreased perfusion in the ischemic area due to increased sympathetic activity. These secondary injuries that occur in TBI can be avoided by the sympatholytic effects of dexmedetomidine.[33] exmedetomidine has been successfully used in neurosurgery (e.g. tumors, decompression). Aryan et al did a retrospective and

descriptive study from 39 neurosurgery patients who received dexmedetomidine and recorded the effects on systemic and cerebral hemodynamics. They found it to be a safe and effective drug.[34]

At recommended doses, dexmedetomidine has been shown to decrease CBF and $CMRO_2$.[35,36] This neuroprotective effect is supposed to be due to activation of alpha2A adrenergic receptor subtype.[37] Due to its sympatholytic and nociceptive properties it is useful in functional neurosurgery as well.

ISSUES WITH PROLONGED DEXMEDETOMIDINE INFUSION

There are a lot of concerns expressed over prolonged use of dexmedetomidine infusion for sedation in ICU patients e.g. rebound hypertension and tachycardia, due to which many intensivists did not use it for more than 24 hours. However now it is being used popularly as a long duration sedative in medical and surgical care units successfully.

Guinter et al conducted a literature review which involved 11 studies, 6 studies in adults and 5 studies in pediatric patients. They found no withdrawal effects in the form of tachycardia or hypertension on discontinuation of the infusion. On the other hand, the incidence of delirium was less as compared to that seen with narcotic or propofol infusions.[38] Kunisawa et al also felt after reviewing literature in which dexmedetomidine was used on a prolonged basis that it was safe as a long term sedative which reduces the use of conventional agents and can be used in patients in whom traditional sedatives are inadequate. The infusion need not be stopped if extubation is planned.[39]

Tobias et al felt that after 4-5 days of dexmedetomidine infusion, it shouldn't be stopped abruptly. Instead slow tapering may prevent the withdrawal effects described in literature.[40] The advantage of dexmedetomidine is that it need not be stopped during weaning like benzodiazepines and narcotics.

CONCLUSION

Due to its desirable properties, e.g. lack of respiratory depression, ease of sensorium and neurological assessment with ongoing infusion, no active metabolites and sympatholysis, we think dexmedetomidine is an ideal drug as a sole sedative agent in patients with TBI. However it should be used carefully it elderly patients and in patients with hepatic and renal dysfunction. TBI with polytrauma renders a patient in a hypovolemic state where cerebral blood pressure (CBP) can be compromised if dexmedetomidine is not used judiciously. Such patients can be managed with fluid resuscitation and by avoiding a loading dose of dexmedetomidine.

Current literature supports use of dexmedetomidine for more than 24 hours which is an advantage as patients with TBI require sedation and ventilation in ICU for neurological improvement.

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