RESEARCH ARTICLE

Cognition State Evaluation by N-back in Mustard Gas Casualties: Dexmedetomine versus Remifentanil in Cataract Surgery

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Background: Sulfur Mustard (SM) is an alkylating agent that has been used as a chemical warfare gas during World War II and by Iraqi army in the Iran-Iraq conflict between 1983 and 1988. SM can cause serious organ damages especially ocular, neurologic, coetaneous, bone marrow and pulmonary complications. On the other hand dexmedetomidine is a α2 agonist with sedative and analgesic effect with a short duration half-life. Considering these benefits, usage of dexmedetomidine would be a good choice in ophthalmic outpatient's surgeries to keep the cognition state in an acceptable condition comparing with other available drugs especially in patients with concurrent chemical burn injury.

Methods: After informed consent, patients with inclusion criteria were randomly divided in to two groups: dexmedetomidine (group D, n=50) and Remifentanil (group R, n=50). Cardiovascular signs, Mini Mental State Examination (MMSE) score were recorded as baseline. Patients received respectively dexmedetomidine by infusion with a loading dose of 0.5µg/kg (during 10 minutes) in group D. The maintenance dose of 0.2µg/kg/hr was then started. Loading dose of remifentanil was given by 0.1µg/kg (during 10 minutes); 5 minutes before local anesthesia in group R and maintenance dose of 0.05µg/kg/min was then started. In Post Anesthesia Care Unit (PACU) after 120 minutes of stopping drug infusions n-back and MMSE tests were performed.

Results: The MMSE score had no statistically difference between two groups before surgery (in subgroup age>=65 P= 0.5, and in subgroup age<65 P= 0.6) but in the PACU the score diverged statistically between two subgroups in age>=65 and age<65 years old respectively (in subgroup age>=65 P<0.0001, and in subgroup age<65 P= 0.03). The results of n-back test showed a more precision and rapidity in working memory in group D. (p<0.001 and p=0.002 respectively).

Conclusion: The result of n-back and MMSE revealed that the cognition state improves better in patients receiving dexmedetomidine comparing with those of remifentanil. Dexmedetomidine is safe for protecting the cognition state especially in patients with borderline respiratory reserve due to chemical burn injury.

Keywords: mustard gas; cognition state; n-back; Mini Mental State Examination

Sulfur Mustard is a very toxic vesicant that has been used as a chemical warfare agent. The severity of injury related to the dose and period of exposure. SM cause organ injuries like ocular and pulmonary complication [1-2]. lung is the main target of SM. acute and late effects have been both stated after exposure to SM. novel approache in anesthesia is needed to have the minimum effects on pulmonary system. Cataract surgery is a common surgery that could be performed under monitored anesthesia care (MAC) with or without local anesthesia [1-2]. With sedoanalgesia, the patient is cooperative and physical reflexes are intact, so resulting in quick emerging and improved operative effectiveness, patient's comfort, pleasure, and reliability [3-4]. Comparing with general anesthesia sedoanalgesia is a chosen method of day-case anesthesia [5]. In the elderly, post-operative cognitive dysfunction is a common problem after main surgery. However, the precise pathogenic mechanism is unidentified. Inflammatory response of hippocampus gland and neuronal apoptosis may cause to Postoperative Cognitive Dysfunction (POCD), and selective alpha 2 adrenal receptor excitation has a caring role. Dexmedetomidine, as a selective alpha 2 adrenal receptor agonist, has a role to protect the brain [6]. Remifentanil, a potent ultra-short-acting mu-receptor agonist is ordered intravenously and used for pain relief and anesthesia. Remifentanil shows some distinct

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pharmacokinetic structures. In tissues and plasma, it is metabolized by esterase organ-independently. Moreover, the onset of action is rapid (± 1.5 minute) and does not gather in the body therefore, lessening the risk of opioid-induced respiratory depression and contributing in a short and anticipated drug effect window. These exceptional structures set remifentanil apart from other opioid agents and make this agent appropriate for the study of the cerebral mechanisms of the opioid system [7]. Anesthetics have effects on all the body parts and systems but the principal effects are on the nervous system. Post-anesthesia complications affect the cognitive functions in different degrees. In general anesthesia, quick retrieval of mental status is a significant target for anesthesiologists. Determining post-operative cognitive functions can measure the level of recovery or mental status alterations caused by anesthesia and surgery [8]. Some neuro-pathophysiological studies have recommended that POCD might even have some mechanisms with Alzheimer's disease through disclosure of plasma β amyloid and Tau phosphorylation [9-10]. Working memory has been defined and debated in several ways: as a cognitive system for the transitory storage and manipulation of recalled data. This part of memory saves data briefly and is essential for cognitive activities [11]. N-back task is one of the most common trial patterns for functional neuroimaging studies of working memory. Subjects are requested to monitor the character or setting of a series of verbal or nonverbal stimuli and to specify whether the currently offered stimulus is the same as the one showed in previous trials [12]. Patients with restrictive lung disease caused by chemical burn injury, especially those as a long time effect of mustard warfare usually have difficulties in usage of sedative agents. Any unreasoned or improper use of drugs may cause serious unpleasant results. So any efforts must be in mind to reduce risk or respiratory problems in these patients.

In this randomized double blind study, by using two cognitive function tests (n-back, MMSE), we intended to observe whether the use of dexmedetomidine for sedation in cataract surgery was associated with a lower incidence of neurocognitive dysfunction in elderly when compared to remifentanil. We also assume that dexmedetomidine by its analgesic and sedative effect can help to fixed hemodynamic fluctuations and oxygen saturation in patients with mustard gas bronchitis to some extent.

Methods

This double blind randomized controlled trial was planned and carried out in mustard gas casualties candidate for cataract surgery under local anesthesia in Labbafinejad medical center between 2014-2015. Mustard gas casualties in Iran-Iraq war aged 40-70 years old, ASA Class I, II with operation time less than one hour were enrolled. Those with initial MMSE<23, any history of psychotic conditions, head trauma and drug abuse were excluded. Patients were randomly allocated to two groups (n=50); group R (Remifentanil) and group D (Dexmedetomidine). Age and sex as demographic data were recorded. Baseline cardiovascular parameters including blood pressure (BP), heart rate (HR), mean arterial pressure (MAP) and O2 saturation were documented.

Functional memory as a cognitive system for the temporary storage and manipulation of remembered information was assessed by n-back test, one of the most popular experimental paradigms for functional neuroimaging studies of working memory [12]. Subjects were asked to monitor the identity or location of a series of auditory stimuli and to indicate when the currently presented stimulus is the same as the one presented in trials previously. If stimulation was like the two previous stimuli, patient pressed key 1 otherwise key 2. For each correct answer 1 point was given and each wrong answer had -0.5 point. Mini-Mental state examination (MMSE) was performed too to assess POCD. MMSE included orientation, memory, attention, calculation, recollection and linguistic ability. The score ranged 0-30.scores <23 considered as POCD.

Five minutes before local anesthesia was given, dexmedetomidine was infused in a loading dose of 0.5μg/kg (during 10 minutes) in the group D. The maintenance dose then with 0.2μg/kg/hr was started. During the procedure, Bispectral index (BIS) was kept between70-80. If it dropped down then the maintenance dose was decreased to 0.1μg/kg/hr and with increasing BIS the drug dose was increased to 0.4μg/kg/hr. Loading dose of remifentanil was given 0.1μg/kg (during 10 minutes); 5 minutes before local anesthesia in the group R and maintenance dose by 0.05μg/kg/min was started. During the procedure, BIS was preserved between 70-80. With decreasing BIS the drug dose declined to 0.025μg/kg/min and with increasing BIS the drug dose augmented to 0.1μg/kg/min.

Vital signs such as respiratory rate (RR), oxygen saturation (SpO2), blood pressure (BP) and heart rate (HR) were measured before anesthesia and every 5 minutes during surgery. All the patients received 5 Lit/min oxygen with oxygen mask. Situations like hypoxia, bradycardia, tachycardia, pain, vomiting and anxiety were treated with appropriate medications. Bradycardia (HR<40 for one minute) and tachycardia (HR>100 for one minute) were treated by 0.5 mg atropine and 0.1 mg propranolol (up to max dose 1 mg) respectively. Hypotension (MAP<60 mmHg for one minute) and hypertension (MAP>120 mmHg for one minute) were treated by 10 mg ephedrine and 50 μg TNG respectively. Since the patient were affected by mustard gas and bronchitis existed to some degree, oxygen with mask was inserted for all patients to keep spo2>92%. Surgery was started at BIS 70-80. Heart rate, MAP and SpO2 were recorded every 5 minutes. At the end of surgery drug administration was stopped and patients were transferred to recovery room. In recovery room after 120 minutes MMSE and N-back tests were performed.

Data were analyzed with SPSS version 21 software. Data are presented as mean±SD, numeric data are presented as percentage (%). The correlation analysis was made with Pearson analysis. P<0.05 was considered statically significant. T-test and Mann-Whitney tests were done for analyzing parametric and non parametric variables.

Results

In this study, 100 patients were enrolled and randomly divided in two groups. Fifty patients were located in dexmedetomidine group (D) and 50 patients in remifentanil group(R). No significant differences were found between the age, gender, ASA and operation time (P=NS).Heart rate, MAP and SpO2 before surgery in both groups were the same (P=NS) (Table 1-2).

MAP and heart rate significantly were lower in

dexemedetomidine group than remifentanil group during and after surgery, but there was no difference in O2 saturation between two groups (Table 3).

No significant difference was seen in preoperative MMSE score between two groups while postoperative MMSE score in dexmedetomidine group was more than in the remifentanil group (Figure 1-2).

N-back task was analyzed by t-test to compare functional memory. Accuracy of functional memory in dexemedetomidine group was better than remifentanil group (P<0.001). Rapidity of functional memory was higher in dexemedetomidine group than remifentanil group (P=0.002). Patients in dexemedetomidine group spent less time to answer comparing to remifentanil group (P=0.03). Patients in dexmedetomidine group spent less time to answer the questions and the rapidity of working memory in dexemedetomidine group was even higher than remifentanil group(P=0.03, Table 4).

Table 1- Demographic and anthropometric data of groups

Variables	Group D	Group R	P
Age	50.26+9.44	51.9+10.02	0.621
Weight	69.00+5.63	70.46+6.64	0.09
Sex	30/20	26/24	0.123
Duration of surgery	35.03+7.62	37.73+6.29	0.411

Table 2- Preoperative comparison of heart rate (HR, beat/min), mean arterial pressure (MAP, mmHg) and 02 saturation

Variables	Group D	Group R	P
Pulse rate	73.3+5.2	73.1+4.5	0.61
MAP	96.3+5.5	95.2+6.6	0.37
O2 Saturation	98.4+0.5	98.5+0.5	0.38

Table 3- Postoperative comparison of heart rate (HR, beat/min), mean arterial pressure (MAP, mmHg) and 02 saturation

Variables	Group D	Group R	P
Pulse rate	65.4+7.6	72.1+4.5	0.009
MAP	76.3+5.4	85.2+8.6	0.01
O2 Saturation	98.8+0.6	98.9+0.9	0.7

Table 4- Accuracy and speed of reaction in N-back test

Variables	Group R	Group D	P
Accuracy	42.05+1.76	45.65+2.96	<0.001
Reaction speed	1.62	1.29	0.03

Figure 1- MMSE score in patients older than 65 years old

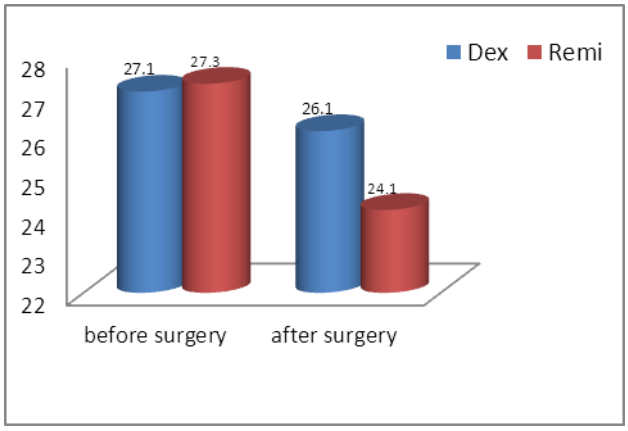
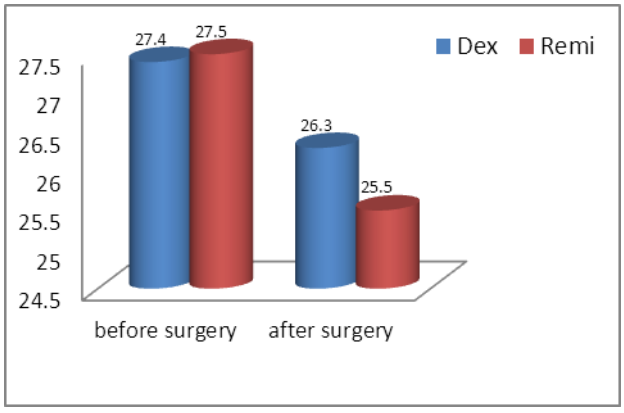


Figure 2- MMSE score in patients younger than 65 years old



Discussion

In monitored anesthesia care, depending on the dosage of anesthetic medications used, sedation level may spread beyond the planned level, even result in general anesthesia, and cardiorespiratory depression may happen. In order to avoid such problem, patients should be monitored closely [3]. In this study all patients were monitored before and after the drug infusions with ECG, SpO2, BIS, noninvasive MAP and with ECG, MAP and SpO2, in the recovery room.

Sedation under monitored anesthesia care with dexmedetomidine kept the conscious sedation and analgesia at suitable level in all patients scheduled for cataract surgery comparing in terms of hemodynamic, sedation, analgesia, postoperative cognitive functions, and recovery. However, the dexmedetomidine group had less postoperative cognitive function disturbance. Heart rate and MAP were lower in the group D than the group R that could be due to diminished sympathetic response and circulatory catecholamine in this group. The n-back task, rather than complex extent, is a main measure in surveys of the neurological substrates of immediate memory. N-back tasks are continuous-recognition measures that demonstrate stimulus sequences, such as images or letters; for each item in the order, people evaluate whether it matches the one showed n items ago. N-back has face validity as a working memory (WM) task because participants must keep and update a dynamic practice set while answering to each item [13].

This study showed that, in dexmedetomidine group, the working memory kept unchanged, the time spent to answer

the n-back task was less and the rapidity of working memory was higher comparing with remifentanil group. in this regard no previous study was performed to compare the results. Moreover; sedation with dexmedetomidine cause less cognitive function disturbance comparing with remifentanil. Arain and Ebert showed the same results when compared the hemodynamic changes between dexmedetomidine and propofol for sedation in surgery under local anesthesia [14].

The elderly patients are at risk of cognitive dysfunction. The nature of POCD is subtle so it might be recognized only by the patient's relatives. Therefore, for its detection, neuropsychological exam is required [15]. In several ways, early cognitive dysfunction may affect the recovery period. Hospital discharge and return to work maybe postponed due to delayed physical and emotional rehabilitation. Also, it can affect the accelerated care plans, which encourage a shorter hospital stay and quick independence. These complications may be incorrectly attributed to drugs or complications of surgery and anesthesia [16]. On the first day after general anesthesia, it can lonely cause weak cognitive dysfunction. Under general anesthesia, Cognitive function in mice with splenectomy was significantly worsened at the first and third days after surgery, dexmedetomidine considerably enhanced the cognitive function. In hippocampus, the expression of IL-1β, TNF-α, Bax and caspase-3 increased after splenectomy. Dexmedetomidine significantly inversed these changes [6].

Different studies showed that POCD is a result of anesthesia. Egi et al., Ni et al. and Jing et al. showed that duration of anesthesia and dose of anesthetic drugs affect the cognitive function while Wei et al. reported that different anesthetic drugs had different effects on cognitive function [17-19]. POCD described as a condition in which post-operative MMSE score decreased 2 or more points comparing before surgery. In this study, preoperative MMSE score was not significantly different between two groups while postoperative MMSE decreased significantly in remifentanil group. Meanwhile dexmedetomidine revealed no statistical difference in postoperative MMSE score. These results were compatible with William-Russo et al. study which showed that there was no POCD after epidural anesthesia under controlled hypotension with dexmedetomidine [20]. Townes et al. reported no decrease in MMSE in young patients after induced hypotension [21]. In our study we used MMSE test for assessment of cognitive function in patients. MMSE is a valid, easy and short test that can be used at bed side.

Maghwry et al. compared the effects of dexmedetomidine and esmolol on brain oxygen saturation in patients that underwent controlled hypoventilation for shoulder arthroscopy. One of the reasons of cognitive disorders is decreased brain blood flow during hypotension. Brain blood oxygen monitoring is not a routine monitoring during anesthesia. no significant difference in MMSE score was reported between two groups before and after surgery because of saving brain blood oxygenation during surgery even with controlled hypotension (55mmHg < MAP < 65 mmHg). They stated that dexemedetomidine is a safer drug than esmolol [22].

For a broad range of surgical procedures under MAC, DEX is an effective usual sedative providing better patient satisfaction, less respiratory depression and less opioid requirements, comparing with placebo rescued with fentanyl and midazolam [23]. Our results were in contrast to the findings of Mohamed et al. who could not verify that Dexmedetomidine infusion can be a helpful adjuvant in general anesthesia to reduce risk of POCD [24]. Removing the confounding factors is a matter of concern in this study. These factors include demographic variations, comorbidities and drug abuse history. The inability to follow up the patients was the limitation we faced in this study because all patients were discharged 6 hours post operation.

Conclusion

This study showed that dexemedetomidine is a safe drug for saving cognitive function and hemodynamic state in mustard gas veterans. It might be due to its analgesic, sedative and anxiolytic effects. Anxiety is an important factor in cognitive disorders.

References

1. Kermany MP, Soltani MH, Ahmadi K, Motiee H, Rubenzadeh S, Nejati V. The impact of anesthetic techniques on cognitive functions after urological surgery. Middle East J Anaesthesiol. 2015; 23(1):35-42.
2. Balali-Mood M, Hefazi M. Comparison of early and late toxic effects of sulfur mustard in Iranian veterans. Basic Clin Pharmacol Toxicol. 2006; 99(4):273-82.
3. White PF, Freire AR. Ambulatory (outpatient) anesthesia: Anesthesia. In: Miller RD, editor. Miller's Anesthesia. 6th ed. Philadelphia: Churchill Livingstone; 2005. pp. 2589–637
4. Morgan GE, Mikhail MS, Murray MJ, Larson CP. 3rd ed. New York: McGraw Hill; 2002. Clinical anesthesiology; pp. 882–8.
5. Birch BR, Anson KM, Miller RA. Sedoanalgesia in urology: A safe, cost-effective alternative to general anaesthesia. A review of 1020 cases. Br J Urol. 1990; 66(4):342-50.
6. Qian XL, Zhang W, Liu MZ, Zhou YB, Zhang JM, Han L. Dexmedetomidine improves early postoperative cognitive dysfunction in aged mice. Eur J Pharmacol. 2015; 746:206-12.
7. Quaedflieg CW, Münte S, Kalso E, Sambeth A. Effects of remifentanil on processing ofauditory stimuli: a combined MEG/EEG study. J Psychopharmacol. 2014; 28(1):39-48.
8. Mashour GA, Forman SA, Campagna JA. Mechanisms of general anesthesia: From molecules to mind. Best Pract Res Clin Anaesthesiol 2005; 19(3):349-64.
9. Fodale V, Santamaria LB, Schifilliti D, Mandal PK. Anaesthetics and postoperative cognitive dysfunction: a pathological mechanism mimicking Alzheimer's disease. Anaesthesia, 2010; 65(4):388-95.
10. Evered LA, Silbert BS, Scott DA, Maruff P, Laughton KM, Volitakis I, et al. Plasma amyloid beta42 and amyloid beta40 levels are associated with early cognitive dysfunction after cardiac surgery. Ann Thorac Surg. 2009; 88(5):1426-32.
11. Ardila A. Language representation and working memory with bilinguals. J Commun Disord. 2003; 36(3):233-40.
12. Owen AM, Mc Millan KM, Laird AR. N-Back working Memory Paradigm: A Meta-Analysis of Normative Function Neuroimaging studies. Human Brain Mapping. 2005; 25:46-59.
13. Kane MJ, Conway ARA, Miura TK, Colflesh GJH. Working Memory, Attention Control, and the N-Back Task: A Question of Construct Validity. Journal of Experimental Psychology. 2007; 33(3):615-22.
14. Arain SR, Ebert TJ. The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. Anesth Analg. 2002; 95(2):461-6.
15. Seymour DG, Severn AM. Cognitive dysfunction after surgery and anaesthesia: What can we tell the grandparents? Age Ageing. 2009; 38(2):147-50.
16. Rödig G, Rak A, Kasprzak P, Hobbhahn J. Evaluation of self-reported failures in cognitive function after cardiac and non-cardiac surgery. Anaesthesia. 1999; 54(9):826-30.
17. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, et al. Hypoglycemia and Outcome in Critically Ill Patients. Mayo Clin Proc. 2010; 85(3): 217-24.
18. Ni X, Martin-Caraballo M. Differential effect of glutamate receptor blockade on dendritic outgrowth in chicken lumbar motoneurons.

Neuropharmacology. 2010; 58(3):593-604.
19. Weinbroum AA, Szold O, Ogorek D, Flaishon R. The midazolam-induced paradox phenomenon is reversible by flumazenil. Epidemiology, patient characteristics and review of the literature. Eur J Anaesthesiol. 2001; 18(12):789-97.
20. Williams-Russo P, Sharrock NE, Mattis S, Liguori GA, Mancuso C, Peterson MG, et al. Randomized trial of hypotensive epidural anesthesia in older adults. Anesthesiology. 1999; 91(4):926-35.
21. Townes BD, Dikmen SS, Bledsoe SW, Hornbein TF, Martin DC, Janesheski JA. Neuropsychological Changes in a Young, Healthy Population after Controlled Hypotensive Anesthesia. Anesth Analg. 1986; 65(9):955-9.
22. Maghawry KM, El-Agamy AES, Tahir WI, Zein AF. Cerebral oxygen saturation monitoring during hypotensive anesthesia in shoulder arthroscopy: A comparative study between dexmedetomidine and esmolol. Egyptian Journal of Anaesthesia. 2015; 31(1):43-52.
23. Candiotti KA, Bergese SD, Bokesch PM, Feldman MA, Wisemandle W, Bekker AY. Monitored anesthesia care with dexmedetomidine: a prospective, randomized, double-blind, multicenter trial. Anesth Analg. 2010; 110(1):47-56.
24. Mohamed S, RamzyShaaban A. The effect of Dexmedetomidine on the incidence of postoperative cognitive dysfunction in elderly patients after prolonged abdominal surgery. 2014; 30(4):331-8.