Perioperative Dexmedetomidine Infusion might improve Postoperative Cognitive Function Recovery in Traumatic Brain Injury Patients

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Abstract

Background: Traumatic brain injury (TBI) might be associated with postoperative (PO) disturbed cognitive function (CF). However, this may be ameliorated on using of anesthetic with preventive ability.

Objectives: To evaluate the outcomes of patients undergoing emergency craniotomy who received perioperative dexmedetomidine (DEX) versus plain saline infusions as a placebo.

Patients and methods: 76 patients were randomly divided into DEX and P groups; DEX loading dose (0.6-µg/kg) was followed by DEX infusion 0.3-ml and 0.1-ml/kg/h during and for 24-h PO. Blood samples (S1-3) were collected for ELISA estimation of serum levels of interleukin (IL)-6, tumor necrosis factor-α (TNF-α), malondialdehyde (MDA), and superoxide dismutase (SOD)**.** CF was assessed 48-hr, 1-wk, 2-wk, and 4-wk PO using the Mini-Mental State Examination (MMSE)**.**

Results: At end of surgery, heart rate (HR) was significantly lower with DEX, while mean arterial pressure (MAP) was significantly lower in all patients with significantly lower MAP measures with DEX. Serum levels of TNF-α, IL-6, and MDA were increased; while SOD levels were decreased with placebo than with DEX infusions. Patients' frequency among CF impairment grades and mean MMSE score showed significant differences in favor of DEX till 4-wk PO. Statistical analyses defined high serum levels of TNF-α and MDA in S3 samples at 24-h as the significant sensitive predictors for low MMSE score at 48-h PO.

Conclusion: TBI-induced inflammatory and oxidative stresses impaired CF that were aggravated by surgery. Perioperative DEX infusion ameliorated the inflammatory and oxidative responses to surgery for TBI and significantly improved CF to placebo infusion.

Keywords: Traumatic brain injury; Dexmedetomidine; Cognitive function; Inflammatory cytokines; Oxidative stress.

DOI: 10.21608/svuijm.2023.181959.1476

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Received: 29 November,2022.

Revised: 23December,2022.

Accepted: 8 January,2023.

Cite this article as: Islam A. Shaboob and Ibrahim E.M. Mostafa.(2023). Perioperative Dexmedetomidine Infusion might improve Postoperative Cognitive Function Recovery in Traumatic Brain Injury Patients. *SVU-International Journal of Medical Sciences*. Vol.6, Issue 1, pp: 512- 524 .

Introduction

Traumatic brain injury (TBI) is one of the leading causes of mortality or long-term neurological disability.The pathophysiological mechanisms of TBI included the mechanical effects of trauma that may result in neurological impairment and unfortunately are irreversible **(Büchele et al., 2020)**. TBI is also associated with local inflammation, oxidative stress, and mitochondrial dysfunction with subsequent neuronal cell death, astrocyte proliferation, and microglia activation **(Dyusembekov et al., 2021)**. These secondary effects of TBI are responsible for the development of neurological deficits and cognitive dysfunction following TBI, but fortunately may be preventive effects **(Bemand et al., 2021)**.

Dexmedetomidine (DEX) is a highly selective α2-adrenergic receptor agonist that is characterized by dose-dependent sedative action, analgesic effects, ability to inhibit sympathetic activity, and provision of cardiovascular stability during surgery **(Jiang et al., 2017)**.

Dexmedetomidine preconditioning of animal model of ischemic stroke after middle cerebral artery occlusion, reduced infarction volume, alleviated brain water content and blood-brain barrier damage, enhanced cell activity, decreased cell apoptosis, and improved neurological scores **(Zhou et al., 2021)**. In a cerebral ischemia-reperfusion animal model, DEX improved pathological damage to the cerebral cortex and decreased the modified neurological severity score through inhibition of autophagy and expression levels of associated proteins and decreased nerve cell injury through inhibition of the expression of miR-199a **(Zhu et al., 2021)**. These animal studies showed the neuroprotective actions of DEX, thus the current study tried to evaluate the outcomes of patients assigned for emergency craniotomy for evacuation of traumatic subdural hematoma (SDH) who received perioperative DEX versus plain saline infusions in a prospective placebo-controlled comparative study.

Patients and methods

Design: Prospective randomized comparative double-blinded clinical trial

Setting: Department of Anesthesia, Pain, and ICU, Faculty of Medicine, Benha University

Participants: All patients admitted to the Emergency Department with traumatic head injury either as solitary injury or as a part of multiple traumas were eligible for evaluation. Patients were evaluated by one of the neurosurgical staff at Benha University Hospital and undertake the diagnostic radiological workup to define patients who had SDH requiring emergency interference. These patients were evaluated by one of the authors for fitness for general anesthesia, Glasgow Coma Scale (GCS), ASA grade, hemodynamic status, and the presence of any exclusion criteria

Exclusion criteria: The presence of other trauma needs emergency interference, other associated cranial injuries, premorbid dementia, hearing and visually impairment, communication disorders, autoimmune disease or maintenance on immunosuppressive drugs, renal, cardiac or hepatic disorders. Also, illiterate and uncooperative patients were also excluded from the study.

Inclusion criteria: No age or sex was exempted; patients who had SDH requiring emergency evacuation and were free of exclusion criteria were enrolled in the study. Ten healthy volunteers free of exclusion and inclusion criteria were included in the study as a control group for MMSE and laboratory investigations

Ethical considerations: The study protocol was preliminarily approved by the Local Ethical Committee in Jan 2020 and final approval was obtained after the completion of case collection in July 2022 by RC: 5.7.2022. Patients' consent was obtained from one of the nearest patients' relatives.

Blindness: Intraoperative infusions were prepared by an assistant, not an author, and were labeled by the group label; P and DEX to be given to patients of placebo and DEX groups, respectively. One author was responsible for the conduction of anesthetic procedures including the administration of the IO infusions and taking blood samples, while the other author was responsible for the registration of monitoring data. The clinical pathologist was blinded about the clinical diagnosis and the indications for performing the requested investigations.

Randomization & Grouping: Patients were randomized into two groups using computer software with the 1:1 blocks method and the obtained sequences were applied as cards labeled by group symbol and were provided to the anesthetist who was responsible for applying the anesthetic procedure. Patients were categorized as group P and DEX according to receiving a placebo (plain 0.9% normal saline) or DEX infusion.

Preparation of DEX infusion: Dexmedetomidine was given as a loading dose of 0.6 µg/kg that was diluted to a total volume of 10-cc in a syringe labeled DEX. DEX infusion was prepared to provide 1 µg/kg and was provided at a rate of 0.3 ml/kg/h. Patients in the control group received a loading dose of 10 ccs of normal saline (0.9% w:v) and an infusion of plain saline in a masked bottle.

Anesthetic protocol: All patients received fentanyl as a fixed sedative as a continuous infusion at a rate of 5 µg/kg/h with maintenance of the total dose was in the previously documented range of 20-30 µg/kg **(Robert et al., 2014)**. Anesthesia was induced by propofol 2 mg/kg, rocuronium 0.5 mg/kg, and the loading dose of DEX. Tracheal intubation was aided by gentle tracheal pressure and an endotracheal tube was inserted. After intubation of the trachea, the lungs were ventilated with 100% O_2 in the air using a semi-closed circle system. Patients were adjusted in a semi-sitting position according to the surgical requirements. DEX and placebo infusions were applied at a rate of 0.3 ml/kg/h, ventilation was controlled with a tidal volume of 6-8ml/kg, and the ventilatory rate was adjusted to maintain an end-tidal carbon dioxide (paCO2) of 32-35 mmHg. Intraoperative non-invasive monitoring for mean arterial pressure (MAP) and heart rate (HR) was conducted continuously. Anesthesia was maintained with sevoflurane 1.7 MAC and top-up doses of rocuronium if needed. For intraoperative analgesia of patients of group P, fentanyl 0.1 µg/kg was given, while DEX infusion was adjusted to provide analgesia for patients of group DEX. Muscle relaxant was reversed using neostigmine 0.05 mg/kg with atropine 0.01 mg/kg.

Postoperative (PO) care: Patients were maintained in the semi-setting position and were discharged sedated to PAUC with a sedation score of 3 on the Ramsey sedation score (RSS). DEX and fentanyl infusions were maintained for 24-hr PO at a rate of 0.1 ml/kg/h to provide analgesia and sedation for both groups, respectively.

Evaluation of Cognition Function (CF): Cognitive function was assessed 48-hr, 1-wk, 2-wk and 4-wk PO using the Mini-Mental State Examination (MMSE), which is a 30-point

questionnaire and lower scores indicated cognitive dysfunction (CD) and a score = 25-30 indicates normal CF **(Folstein et al., 1975)**. An Arabic form was prepared by a professional translation center and an assistant who was accustomed to deal with neurologically deficient or handicapped patients was responsible evaluation of CF using the Arabic form.

Blood sampling and Investigations: Three blood samples were obtained immediately before injection of the loading DEX dose, at end of the surgery, and 24-hr PO (S1-3 samples), were collected in plain tubes, allowed to clot in a warm water bath at a temp of 37^{o}C for 5 minutes, and then centrifuged at 5000 rpm for 2 minutes to separate serum that was collected in Eppendorf tubes and stored at -20^{o}C till ELISA estimation of serum levels of interleukin (IL)-6, tumor necrosis factor-α (TNF-α), malondialdehyde (MDA) and activity levels of superoxide dismutase (SOD) using Abcam enzyme-linked immunosorbent assay (ELISA) kits (Abcam Inc., San Francisco, USA; catalog no. ab187013, ab46087, ab233471, ab65354, respectively). The results were read using a 96-well microplate ELISA reader (Dynatech MR 7000).

Statistical analysis

Results were analyzed by One-way ANOVA for analysis of variance, paired t-test, and Chi-square test (X^2 test) using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA). Pearson's correlation analysis was used to assess the relation between MMSE results at 48-h PO and serum levels of studied biomarkers estimated in S3 samples. Regression analysis, using the Stepwise method with multi-module analysis, and the Receiver characteristic curve was used to determine the significant predictors of the estimated biomarkers for 48-h MMSE results. The cutoff point for significance was assumed at a P value of <0.05.

Results

During the study duration, 9 patients were excluded; 4 had multiple head injuries requiring more than SDH evacuation, 3 patients had multiple injuries in the body that required urgent surgical interference and 2 patients were comatose and required admission to ICU and maintained on mechanical ventilation. Seventy-six TBI patients had SDH with depressed bone fragments in 5 patients and free of the depressed bone fragment in 71 patients. These 76 patients were randomly allocated into two groups (**Fig. 1**); there were non-significant differences between patients of both groups as regards preoperative data.

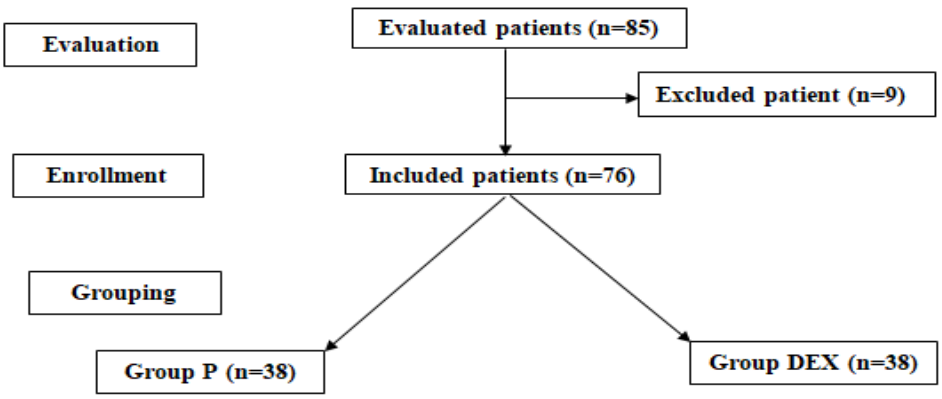

Fig. (1): Study Flowchart

Mean operative time and blood loss were comparable between both groups, while DEX infusion significantly (P<0.001) reduced the intraoperative consumption of fentanyl in comparison to placebo infusion. At the end of the surgery, HR measures were significantly lower (P=0.001) in DEX, while were non-significantly lower (P>0.05) in the P group in comparison to their preoperative measures with non-significant differences between both groups. On contrary, MAP measures were significantly lower at end of surgery in all patients compared to their preoperative measures with significantly lower MAP measures of patients of the DEX group than that of patients of the P group. Operative time and intraoperative blood loss showed non-significant differences between both groups (**Table 1**).

Table 1. Preoperative and Intraoperative data of patients of both groups

Data		**Group P (n=38)**	**Group DEX (n=38)**
Age (years)		47 (±7.4)	48 (±6)
Body mass index (kg/m2)		30.6 (±1.5)	30.2 (±2)
Sex; Male: Female		29:9	31:7
ASA grade; I:II: III		26:9:3	24:12:2
Presence of depressed bone fragments		2 (5.3%)	3 (7.9%)
Heart rate (beat/min)	**Baseline**	78.4±6.9	78.3±4.1
	End of surgery	76±7.4	75±4.6*
Mean arterial pressure (mmHg)	**Baseline**	85±6.7	85.5±6.5
	End of surgery	81.5±6.5*	78.6±5.4†‡
Operative time (min)		129±17	126±15
Blood loss (ml)		430±102.1	412±123.9
Total dose of intraoperative fentanyl (µg/kg)		19.5±1.5	10.5±1.3†

** indicates a significant difference at P<0.05 compared to baseline measures; † indicates a significant difference at P<0.001 compared to baseline measures; ‡ indicates a significant difference at P<0.05 between both groups*

Serum levels of TNF-α and IL-6 increased progressively in the consecutive samples of all patients with significantly lower levels of both cytokines in S2 and S3 samples of patients of the DEX group than in samples of patients of the P group. Serum levels of TNF-α estimated in S2 and S3 samples of patients of the P group were significantly (P=0.0003 & <0.001) higher than levels estimated in S1 samples with non-significantly higher serum levels of TNF-α in S3 than in S2 samples of these patients. On contrary, in samples of patients of the DEX group the differences were non-significant despite the progressively increased levels. On the other hand, serum levels of IL-6 estimated in S2 and S3 samples of all patients were significantly (P<0.001) higher than estimated levels in S1 samples with significantly higher levels in S3 samples than in S2 samples of patients of both P group (P<0.001) and DEX (P=0.0013) group (**Table 2, Fig. 2**).

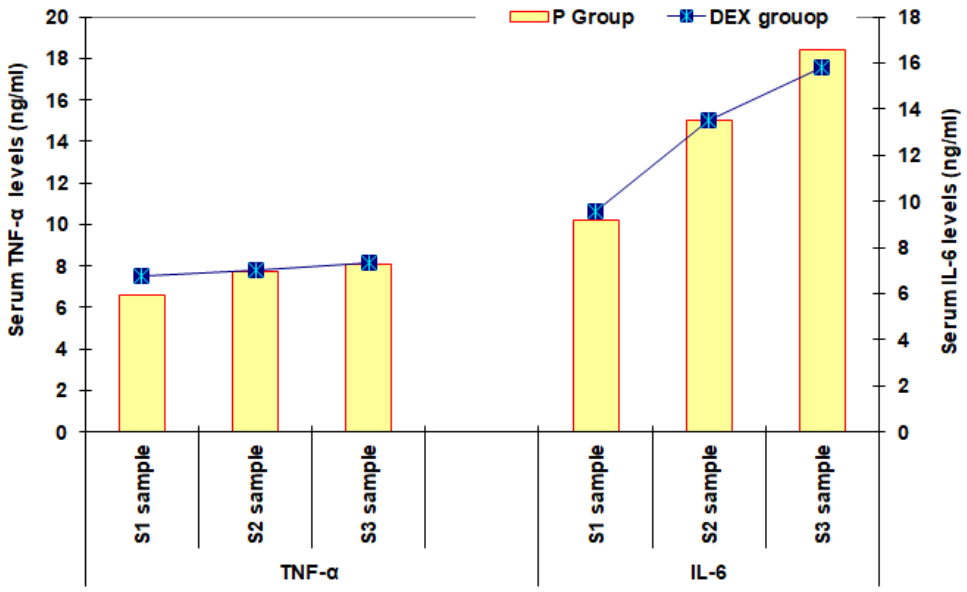

Fig. (2): Mean serum levels of TNF-α & IL-6 estimated in samples of the patients of both groups (S1: Preoperative; S2: End of surgery; S3: 24-h PO)

Serum levels of TNF-α, IL-6, and MDA were 0.078 (±0.009 ng/ml), 0.01 (±0.004 ng/ml), and 0.515 (±0.186 nmol/ml), respectively, and serum activity levels of SOD was 0.486 (±0.146 IU/L) in samples of volunteers. Patients of the P group showed a progressive and significant increase of serum MDA and a decrease of SOD levels in the three successive samples with a significant difference in comparison to corresponding levels estimated in samples of patients of the DEX group. On the other hand, serum levels of MDA and SOD activity levels were significantly decreased and increased, respectively in the successive samples of patients of the DEX group (**Table 2, Fig. 3**).

Table 2. Serum levels of TNF-α, IL-6, and MDA, and activity levels of SOD estimated in the three samples of patients of both groups

Parameters		Group P (n=38)	Group DEX (n=38)	P value
TNF-α (ng/ml)	S1	6.6±1.32	6.78±1.65	0.601
	S2	7.72±1.23	7.05±1.61	0.045
	P1 value	0.0003	0.472	
	S3	8.09±1.2	7.315±1.64	0.022
	P1 value	<0.001	0.161	
	P2 value	0.139	0.479	
IL-6 (ng/ml)	S1	10.2±2.79	9.6±3.6	0.419
	S2	15±2.68	13.5±3	<0.001
	P1 value	<0.001	<0.001	
	S3	18.4±3.16	15.8±2.97	0.0004
	P1 value	<0.001	<0.001	
	P2 value	<0.001	0.0013	

MDA (nmol/ml)	**S1**	1.31±0.15	1.28±0.18	0.541
	S2	1.5±0.22	1.216±0.15	<0.001
	P1 value	0.0002	0.106	
	S3	1.76±0.19	1.14±0.15	<0.001
	P1 value	<0.001	0.0004	
	P2 value	<0.001	0.030	
SOD (IU/L)	**S1**	1.37±0.13	1.36±0.19	0.749
	S2	1.24±0.14	1.5±0.18	<0.001
	P1 value	0.0001	0.0015	
	S3	1.12±0.11	1.7±0.16	<0.001
	P1 value	<0.001	<0.001	
	P2 value	0.0001	<0.001	

* indicates a significant difference at P<0.05 compared to baseline measures; † indicates a significant difference at P<0.001 compared to baseline measures; ‡ indicates a significant difference at P<0.05 compared to placebo group

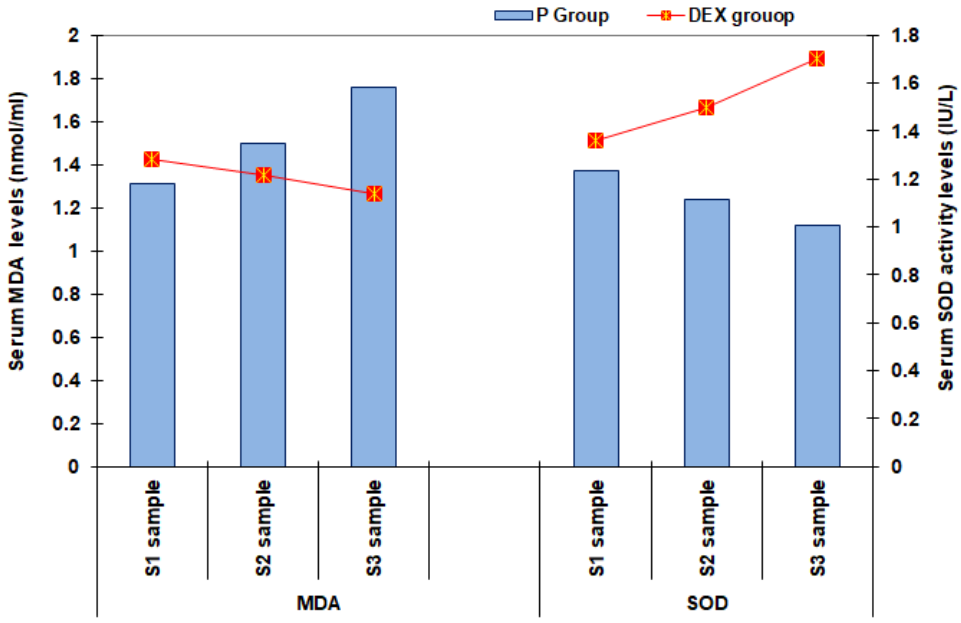

Fig. (3): Mean serum levels of MDA & SOD activity levels estimated in samples of the patients of both groups (S1: Preoperative; S2: End of surgery; S3: 24-h PO)

At 48-h PO only 7 patients (9.2%) had within normal MMSE and were considered to have normal CF with a non-significantly higher frequency of patients had normal CF among patients of the DEX group. The frequency of patients among CF impairment grades and mean MMSE score showed significant differences between both groups in favor of the DEX group during PO follow-up till 4-wk PO (**Table 3**).

Table 3. Distribution of patients of both groups among grades of CF impairment and mean MMSE score during follow-up till 4-wk PO

	Distribution among CF impairment grades				**MMSE score**		
Time	**CF status**	**P group**	**DEX group**	**P value**	**P group**	**DEX group**	**P value**
48-h PO	**Normal**	2 (5.3%)	5 (30.3%)	0.0375	17.6±3.9	20±4	0.011
	Mild	9 (23.7%)	21 (53.9%)				

	Moderate	27 (71%)	12 (15.8%)				
1-w PO	**Normal**	4 (10.5%)	8 (21.1%)	0.018	19.5±3.7	22±3.3	0.0068
	Mild	13 (34.2%)	21 (53.9%)				
	Moderate	21 (55.3%)	9 (23.7%)				
2-w PO	**Normal**	8 (21.1%)	11 (28.9%)	0.023	21±3.5	22.7±3.3	0.028
	Mild	19 (50%)	25 (65.8%)				
	Moderate	11 (28.9%)	2 (5.3%)				
4-w PO	**Normal**	19 (50%)	29 (76.3%)	0.03	23.9±3.8	26.2±2.7	0.003
	Mild	16 (42.1%)	9 (23.7%)				
	Moderate	3 (7.9%)	0				

** indicates a significant difference at P<0.05 compared to baseline measures; † indicates a significant difference at P<0.001 compared to baseline measures; ‡ indicates a significant difference at P<0.05 compared to placebo group*

The mean value of the MMSE score of volunteers was 28.5 (±1.4). At 48-h PO, MMSE score was negatively correlated with serum levels of IL-6 (r=-0.532, p<0.001), TNF-α (r=-0.466, p<0.001), and MDA (r=-0.353, p=0.002), while showed positive significant correlation the serum activity of SOD (r=0.494, p<0.001) estimated in S3 samples at 24-h PO. Further, at 48-PO, MMSE was positively correlated with the administration of perioperative DEX infusion (r=0.291, p=0.011). ROC curve analysis defined high serum levels of TNF-α and MDA in S3 samples at 24-h PO as the significant sensitive predictors for low MMSE score at 48-h PO (**Fig. 4**), while Regression analysis defined high serum IL-6 and low serum activity of SOD in S3 samples as the significant predictors for low MMSE score at 48-h PO (**Table 4**).

Table 4. Statistical analyses of the lab parameters estimated in the S3 sample at 24-h PO as predictors for impaired CF manifested as low MMSE at 48-h PO

	Receiver characteristic curve analysis				**Regression analysis**	
Lab variables	**Area under curve**	**Standard error**	**P-value**	**95% Confidence Interval**	**β**	**P-value**
IL-6	0.394	0.103	0.330	0.192-0.597	0.381	0.001
TNF-α	0.241	0.067	0.017	0.110-0.371	0.195	0.095
MDA	0.263	0.081	0.029	0.105-0.421	0.137	0.244
SOD	0.641	0.068	0.195	0.508-0.773	-0.305	0.006

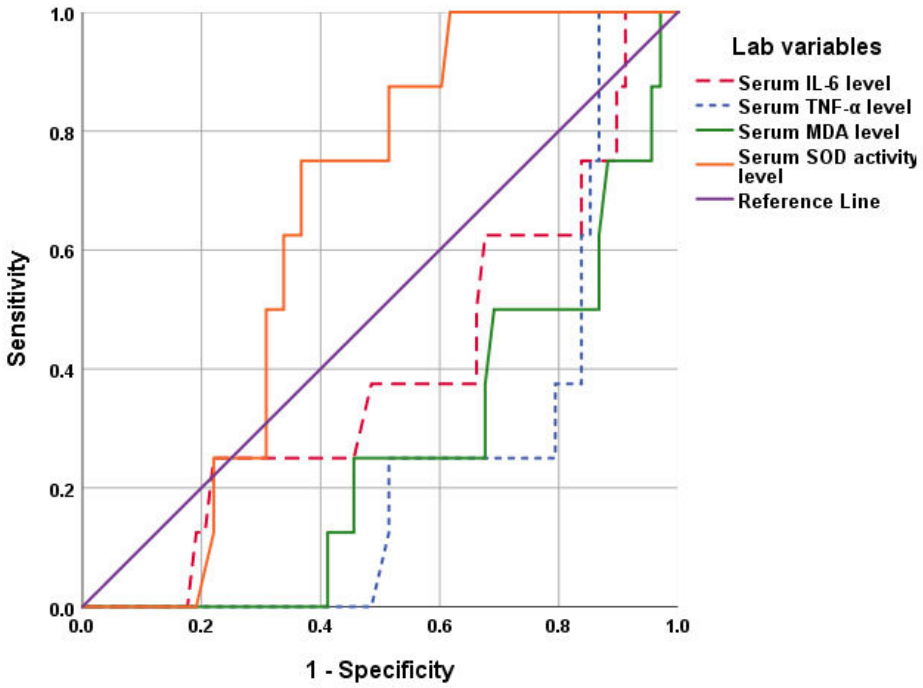

Fig. 4. ROC curve for lab parameters estimated in S3 sample as predictors for CF impairment as judged by MMSE

Discussion

Traumatic brain injury (TBI) is associated with disturbed cognitive function (CF) that is unfortunately worsened by surgical interference as evidenced by the significantly lower MMSE score of patients at 48-h PO compared to the score recorded for the healthy volunteers; these data go in hand with recent animal-model **(Yu et al., 2022)** and clinical studies **(Wong et al., 2018; Ernst et al., 2022; Feiger et al., 2022)** that documented the deleterious effect of TBI and craniotomy CF.

Moreover, TBI-induced immune and redox statuses as evidenced by the significant differences between levels of inflammatory cytokines and measures of oxidative stress before surgery in comparison to volunteers' levels. These stresses were magnified by surgical interference and continued till 24-h PO as evidenced by the reported significant differences between levels estimated in S2 and S3 samples in comparison to S1 samples. Similarly, a recent study concluded that surgical interference for TBI worsens the TBI-induced disturbances in serum levels of inflammatory cytokines as shown by the significant differences in levels of estimated parameters after surgery compared to before surgery **(Woo et al., 2020)**.

However, perioperative DEX infusion till 24-h PO significantly improved the disturbing levels of estimated inflammatory cytokines and oxidative stress variables in comparison to levels estimated in samples of patients of the placebo group. These data supported those recently detected using animal models, where DEX-supplementation was found to suppress the isoflurane-induced cognitive impairment by activating the MEK1/ERK1 pathway that activated the nuclear factor erythroid 2-related factor/Heme Oxygenase 1 pathway which suppressed the isoflurane-induced oxidative stress **(Huang et al., 2022)**, and in an animal model of intestinal ischemia-reperfusion injury

preoperative DEX alleviated neuro-inflammation with reduction of the incidence of CD through reducing serum and hippocampal levels of norepinephrine, IL-1β, TNF-α, and MDA at 24 h after injury with suppression of the expression levels of tyrosine hydroxylase in the locus coeruleus and hippocampal microglia **(Li et al., 2022)**. Further, DEX injection ameliorated the induced cognitive impairment in depressed rats on the use of electroconvulsive therapy through the reduction of neuroinflammation via upregulation of the expression levels of microRNA 146a-5p and inactivating nuclear factor-κB pathway **(Zhou et al., 2022)**.

All patients of TBI showed PO delayed CF recovery that extended till 14-d PO, despite being progressively improving. Perioperative DEX infusion allowed significantly more rapid cognitive function recovery than placebo infusion, both as frequency among MMSE grades and regarding mean MMSE score. These findings go in hand with a recent study that advocated implementing fast-track surgery with the use of DEX to improve cognitive function recovery **(Kong et al., 2022)**. Also, a review of the literature found the vulnerability of elderly adults to PO cognitive dysfunction was exacerbated by poorly controlled PO pain and the use of opioid pain medications and recommended the use of non-opioid medications such as DEX that may provide benefits beyond analgesia **(Wilson et al., 2022)**. Further, a meta-analysis found PO DEX infusion reduced the incidence of POCD compared with propofol and normal saline **(Shang et al., 2022)**. Moreover, a comparative study found DEX supplementation during isoflurane anesthesia for geriatric patients provided higher MMSE scores 1-week PO **(Huang et al., 2022)**.

Statistical analyses defined high serum levels of IL-6, TNF-α, and MDA and low SOD activity in blood samples obtained 24-h after surgery for TBI could predict deteriorated CF as manifested by MMSE evaluated at 48-h PO. Interestingly, the assessed MMSE at 48-h PO was positively and significantly correlated with the use of DEX perioperative infusion. In support of these findings, **Zhang et al., (2020)** detected significantly lower incidence of PO delirium and serum levels of IL-6 and TNF-α over the first 3 days after hip surgery in elderly patients receiving DEX than placebo infusion. Also, **Tang et al., (2020)** reported that combined administration of DEX and sufentanil as intravenous patient-controlled analgesia for patients undergoing non-cardiac surgeries provided better PO analgesia, fewer inflammatory responses, and lower PO delirium scores with better health statuses. Further, **Chen et al., (2021)** found DEX infusion with goal-directed fluid therapy may control neuro-inflammation in adults undergoing cranial surgery without hemodynamic, and **Fondeur et al., (2022)** documented that DEX prevents the development of PO delirium in elderly patients who had the non-cardiac surgical procedure through the suppression of neuroinflammation and reduction of pain scores and improving sleep quality.

Conclusion

TBI-induced inflammatory and oxidative stresses are exacerbated by surgical interference. TBI is associated with impaired CF that was aggravated by surgery. Perioperative DEX infusion ameliorated the inflammatory and oxidative responses to surgery for TBI and significantly improved CF to placebo infusion.

Acknowledgement

The authors provided deep thanks for staff members of Medical

Biochemistry, Faculty, Benha University for conducting the laboratory work.

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