Comparative Study on the Effect of Prime Solution Included Dexamethasone Vs. Methyl Prednisone on Incidence of Postoperative Delirium in Patients with Open Heart Surgery by Cardio Pulmonary Bypass Circuit

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ABSTRACT
Introduction: Delirium is a fluctuating type of cognitive impairment and is common in hospitalized patients and after open heart surgery has been reported up to 90%, which leads to increased risk of dementia and hospitalization costs, reduced quality of life, risk of falls. Needs long-term care and etc. Activation of the deep inflammatory response dependent on the blood response and the cardiopulmonary pump circuit is one possible reason for this. Therefore, in this study, two anti-inflammatory drugs, dexamethasone and methylprednisolone, were used in Prime solution in cardiac surgery patients and then the occurrence of delirium was evaluated.

Methods and Materials: In this clinical trial study with a sample volume size 43 patients in open-heart surgery by on-pump method, after random assignment to two groups including dexamethasone and methylprednisolone that were added to prime solution. Inclusion criteria were EF more than 30%, candidate for mitral valve surgery, absence of cognitive impairment and preoperative delirium and age range 30-65 years. In the first group with 21 patients received dexamethasone at a dose of 0.1 mg/ kg and in the second group with 22 patients at a dose of 0.4 mg/Kg in prime solution. Then delirium examined with standard CAM-ICU instruments after extubation and then the results were analyzed with SPSS 21 version.

Results: The results showed that only 18% of patients who received methylprednisolone primer solution and 28% of patients who received dexamethasone primer solution had delirium, and this difference was non-significant (P. value: 0.448).

Conclusion: In this study, the anti-inflammatory drug methylprednisolone were not superior to each other and had a similar effect on delirium.

Introduction: Delirium is a fluctuating cognitive impairment and a common and acute problem for hospitalized patients. According to the definition (DSM IV-TR), delirium is a type of consciousness and cognitive disorder that occurs within a short period of time and has characteristics such as change in level of

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consciousness, decreased concentration and memory, positioning disorder, rapid onset of several hours to several days, short period and etc also having a significant fluctuation (mostly during the night) (1–3). The incidence of cognitive impairment in patients in inpatient wards is different and the highest rate is after thoracotomy and heart surgery so this rate has been reported up to 90% (4).

Today, despite the improvement of surgical techniques and brain protection strategies, its incidence is still high and is the most common brain injury after heart surgery(5). Glumac et al. (2017) believe that cognitive impairment after heart surgery has widespread and often subtle symptoms that early detection and prevention of their occurrence will lead to faster recovery of the patient, shortening the time to return to society, etc(6).

Incidence of delirium with increasing mortality, prolonged hospital stay, increased hospitalization costs, decreased patient rehabilitation, increased intubation time, increased risk of falling, cognitive impairment, increased risk of dementia, inability to return to work, very low quality of life, And long-term care is associated (7).

The main cause of cognitive impairment in patients after surgery is not clear, but several factors are mentioned in the process of delirium formation, including artherosclerosis, micro embolism, cerebral inflammation, blood-brain barrier disorders, and cerebral hypo perfusion(8,9). In fact, trauma to the body following open heart surgery activates the systemic inflammatory response (SIRS) and predisposes the brain to cognitive decline(9,10). As Denilson (2018) writes: Cardiac surgery is closely related to the deep inflammatory response as well as surgical trauma and the reaction between the blood and the prosthetic surface of the cardiopulmonary pump circuit (11). In the study of Jason et al. (2017), out of 2280 patients undergoing heart surgery, 451 patients reported cognitive impairment, of which 384 had a cardiopulmonary pump (12).

Athens et al. (2014) used dexamethasone in their study on control of delirium after cardiac surgery(13), in the experimental study of Glamek et al. (2018) the use of dexamethasone before surgery led to a reduction in delirium(6). Also, in the study of Ruiz et al. (2017), the use of high dose methylprednisolone (250 mg) reduced delirium after heart surgery(3).

It seems that paying attention to the inflammatory process in the pathology of cognitive disorders is very important. Modulation of the immune system with anti-inflammatory drugs can be a way to reduce inflammation and its complications, so in this study in open heart surgery patients we compared and the effects of these two anti-inflammatory drugs methylprednisolone and dexamethasone.

**Materials and Method:**

This study was a double-blind study is one in which neither the participants nor the experimenters know who is receiving a particular treatment and Statistical analyst was blinded and performed at the Open Heart Surgery Center of Imam Reza Hospital in Mashhad. Inclusion criteria included age range 30 to 65 years, no cognitive impairment and delirium before the start of the study, candidate for mitral valve surgery, EF was more than 30%, as well as cases such as patient return to The operating room, the patient’s prolonged coma, and the individual’s vision or hearing problems were considered as exclusion criteria. The sample size was determined based on the research of Mardani (19) who examined delirium using the “CAM” questionnaire and the formula of two average related to a quantitative variable in two independent communities (also α: 0/05 and β: 0/2) was 21 patients in each group (Due to the possibility of sample loss, more patients were selected and 43 patients remained at the end of study). Then 21 patients in dexamethasone group and 22 patients in methylprednisolone group.

The CAM-ICU standard questionnaire was introduced in 1990 by Inoye et al. It is effective for assessing and recognizing dizziness and monitoring of delirium in patients and can be used in all departments including intensive care. Its sensitivity is 94% and its specificity is 89% (14). And its reliability was reported by Koga (2015) 95%(15).

The method was that after obtaining the ethics license from the ethics committee of
Patients who were eligible for the study were divided into two groups receiving a prime solution containing dexamethasone and methylprednisolone.

Method of anesthesia in patients using midazolam in the amount of 0.05-0.1mg/kg, fentanyl 5-10µg/kg, propofol 1-2 mg/kg and atracurium in the amount of 0.5-0.6 mg/kg and then during anesthesia until the end of surgery, infusion of midazolam at the rate of 5 mg/h and atracurium at the rate of 20 mg/h or propofol 50µg/kg/min was used. After randomly assigning patients to groups, dexamethasone at a dose of 0.1 mg / kg in prime solution and methylprednisolone at a dose of 4.0 mg/ kg in prime solution was used. After the operation, the patients were visited in the ICU. The first visit was performed 4 hours after extubation (first 4 to 6 hours) by an anesthesiologist, perfusion specialist. Then the results were analyzed in IBM SPSS version 21 and statistical chi squer.

Results:
In this study the patient average age in the dexamethasone group was 48 ± 8 and in Methyl prednisolone group was 46 ± 6 which were homogeneous in terms of age according to T-test (P. value = 0. 50). The mean EF was 48.47± 8.37 in the first group and 48.09 ± 6.89 in the second group, which were homogeneous in terms of left ventricular ejection fraction (P. value = 0.87).According to Table 1, the two groups were homogeneous in terms of quantitative variables related to heart surgery (p>0.05.).

According to the Table 2, a total of 10 people had delirium and 33 people did not have delirium after surgery. In fact, at the end, 6 people in the group receiving prime solution containing dexamethasone and 4 people in the group receiving prime solution containing methylprednisolone after surgery were positive for delirium, which according to Chi-square test and P. value (0.448) effect Methylprednisolone and dexamethasone were similarly distant and this effect was not statistically significant and was not superior to each other.

Discussion:
Despite the fact that several decades have passed since the beginning of open heart surgery and the side effects of delirium with it and the failure to completely prevent and treat it, the use of anti-inflammatory steroidal drugs such as dexamethasone and methylprednisolone has always been discussed. We compared the effects of these two drugs with an open heart. In this study, there was no statistically significant difference between the two groups of patients receiving prime solution containing dexamethasone and methylprednisolone and did not have superiority over each other in control of delirium.
The study of meta-analysis of Taiwi et al. (2018) and the study of RCTs that addressed the issue of drug factors and delirium showed that drug factors are significantly effective in reducing the risk of delirium after heart surgery (16).

Clemmesen et al. (2018) in the study of the effect of a single dose of 125 mg of methylprednisolone on delirium after pelvic surgery. It was statistically significant on delirium. In fact, the use of methylprednisolone in the control of delirium after surgery was effective due to the modulation of the immune system. In this study, the samples are older (17). However, attention to dose adjustment of the drug according to weight (in the elderly population) should be considered from the beginning to prevent possible side effects such as infection.

In the study of Deliman et al. (2016), the use of dexamethasone and evaluation one month later of patients with open heart surgery did not have a statistically significant difference in the score of cognitive impairment. Of course, the author himself believes that rational administration of the drug according to age can be useful in reducing the risk of mortality and complications after surgery, but it seems that a period of one month in this area and the involvement of other interfering factors (18).

In the study of Davood Mardani et al. (2012), a significant difference was found in patients receiving dexamethasone at the rate of 8 mg every 8 hours for three days with the control group in terms of delirium. Finally, on the first day, 9.3% of the patients who received dexamethasone and 26% of the control group had delirium. The author believes that the use of low-dose dexamethasone can be useful in reducing the incidence of delirium and faster extrusion of patients and recovery after surgery. Of course, this study was different from our study in terms of mean age and type of surgery; The mean age was 64 years in the drug group and 60 years in the placebo group and the samples were elderly (19, 20).

**Conclusion**

The results of the present study showed that the use of two anti-inflammatory drugs, methylprednisolone and dexamethasone, was effective in controlling delirium after open heart surgery, but they were not superior to each other. Because open heart surgeries are varied and the duration of anesthesia varies, further studies are recommended for larger sample sizes.

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