Comparison of Controlled Hypotension Due to the Use of Dexmedetomidine, Magnesium Sulfate, and Esmolol in Craniotomy Surgery

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Abstract

Introduction: Craniotomy includes the temporary removal of bone flap from calvarium to access the intracranial contents, which is usually used to reduce intracranial pressure. Induced or controlled hypotension is a method by which arterial blood pressure is predictably reduced, thus reducing bleeding. Therefore, the present study aimed to compare the dexmedetomidine, magnesium sulfate, and esmolol in controlled hypotension in craniotomy of patients with brain injury.
Materials and methods: In this randomized double-blind clinical trial, 45 patients entered into study based on inclusion criteria. All patients were monitored when entering operating room. The questionnaire was completed by all groups, in which PR, MAP (Mean Arterial Pressure), mean bleeding score, mean of received packed cells, controlled hypotension and bradycardia, and survival of patients were recorded. Data were analyzed using spss software version 19, and ANOVA and T-Test were used for statistical significance analysis.
Results: The mean age and standard deviations of the three groups of dexmedetomidine, esmolol and magnesium sulfate were 36.78±10.32, 34.47±10.58, and 39.67±11.99 years, respectively. There was no significant difference between the three groups in terms of age, gender, initial heart rate and baseline blood pressure (BP). The MAP and bleeding score (P=0.04 and P=0.0001) was significantly lower in the dexmedetomidine group than in the other two groups. Although the heart rate in the esmolol group was lower than the other two groups, the difference was not significant (P = 0.128). Unlike esmolol and magnesium sulfate groups, GOS did not decrease in the dexmedetomidine group.
Conclusion: Comparison of the three groups in controlled hypotension in craniotomy surgery showed that the MAP and bleeding score of dexmedetomidine group was significantly lower than the other two groups, and the GOS didn't decrease in this group. In general, dexmedetomidine would be a better choice for controlled hypotension in craniotomy.

Key Words: Dexmedetomidine, Craniotomy Surgery, Controlled Hypotension, Esmolol, Magnesium Sulfate.
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Introduction

Craniotomy is the temporary removal of the bone flap from the calvarium to access the intracranial contents. In emergencies, it is commonly used to reduce intracranial pressure in patients with cerebral edema, evacuation of intracranial hemorrhage and abscess (Donovan et al., 2006).
Controlled hypotension simply means reduction of systolic blood pressure to 80-90 mm Hg and the decrease of MAP to 50-60 mm Hg or 30% of baseline arterial pressure.

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Induced or controlled hypotension is a method by which arterial blood pressure is predictably reduced to decrease bleeding, make surgery easier, and to reduce the amount of blood transferred to the patient (Yun et al., 2015, Rodrigo, 1995).
Ideally, a hypotensive agent is expected to be easy to use, have a short onset time, and with effects that disappear immediately after cessation of use without any toxic metabolites. It should also has little effect on vital organs and has dose-dependent and predictable effects. For controlled hypotension, various agents are used including magnesium sulfate, dexmedetomidine, vasodilators (sodium nitroprusside), nitroglycerin, opioids, pregabaline, esmolol, gabapentin, clonidine, ganglionic blockers, magnesium, calcium channel blockers (Khalifa and Awad, 2015) and beta-adrenergic antagonists, though their degree of success varies (Valecha et al., 2016).
Dexmedetomidine is a central alpha-2 adrenergic agonist, short-acting and selective, and is characterized by a dose-dependent reduction in arterial blood pressure, heart rate, cardiac output, and norepinephrine release. It has sedative, analgesic, and anesthetic effects, with properties of sympathetic inhibition. Compared to alpha 1, Alpha 2 selectivity is 8 times higher than that of clonidine. Its function is to bind to pre-synaptic and post-synaptic C-fibers in the dorsal horn of neurons (Mohamed et al., 2015, Lee et al., 2015, Dong et al., 2016, Jin et al., 2017, Lewis et al., 2015).
Esmolol is a selective and extremely short-acting beta-1 adrenergic antagonist. In infusion use and intravenous injection, it has a rapid onset of action. By the time the infusion is complete, the arterial blood pressure will return to its pre-infusion state without creating a hypertensive rebound (Valecha et al., 2016).
Magnesium is another drug with positive effect on postoperative bleeding (Akkaya et al., 2014). Its function is to limit the excretion of calcium from the sarcoplasmic reticulum and create a vasodilator effect by increasing the production of prostacyclin and inhibiting the activity of the enzyme converting angiotensin or ACE. Magnesium reduces the need for painkillers because it is itself an N-Methyl-D-Aspartate receptor antagonist (Mireskandari et al., 2015, Ryu et al., 2009, Shimosawa et al., 2004).
Although previous studies have shown the capability of these drugs to reduce controlled blood pressure during surgery, few studies have compared them specifically in surgery. Similar clinical features of dexmedetomidine and magnesium sulfate, along with a stable hemodynamic response to anesthesia, and significant reduction in HR after administration of dexmedetomidine led to the design of the present study to suggest a more effective drug with fewer side effects (Lee et al., 2015). Therefore, the present study aimed to compare the dexmedetomidine, magnesium sulfate, and esmolol in controlled hypotension in craniotomy of patients with brain injury.

Materials and Methods

This randomized double-blind clinical trial was performed on 45 patients with brain injury, were candidates for craniotomy and referred to Vali-e-Asr Hospital in Arak, Iran. The patients were selected as samples based on inclusion criteria and then were randomly divided into three groups: dexmedetomidine, magnesium sulfate, and esmolol.

Inclusion Criteria

1. Patients candidate for craniotomy surgery due to brain injury.
2. Insensitivity to magnesium sulfate, esmolol, and dexmedetomidine.
3. Surgery performed by a surgeon.

Exclusion Criteria

1. Patient's unwillingness to participate in study.
2. All patients who died during surgery for any reason except bleeding.
3. Preoperative use of magnesium sulfate, esmolol, and dexmedetomidine before surgery.
4. Cardiovascular diseases and hypertension.

Sample size

$$n \geq (\frac{\left[Z_{(1-\alpha/2)} + Z_{(1-\beta)}\right]^2 \ [\sigma_1 + \sigma_2]^2}{(\mu_1 - \mu_2)^2} \approx 16$$

$Z_{(1-\alpha/2)}=1.96$ $Z_{(1-\beta)}=2.33$ $\delta_1=27.8$ $\delta_2=22.7$

$\mu_1=77.1$ $\mu_2=22.7$

n = 16 + 10% (loss) = 15

n total= 15 × 3 = 45

Finally, 45 patients entered into the study based on the inclusion criteria. When entering the operating room, all patients were monitored for heart rate, respiration rate, blood pressure, SPO_2, temperature, gapnography, and ECG. They then received 3-5 cc of crystalloid fluid as CVI, followed by 1 mg of midazolam with 1-2 cc of fentanyl. After that, a line was taken from the non-dominant radial artery of the patients to give the medication.

The patients were anesthetized by injecting fentanyl (2 micro/kg), midazolam (0.3-0.5 mg/kg), atracurium (1-2 mg/kg), and propofol (2-3 mg/kg). They were then intubated and connected to the ventilator, and after prep and drep, were prepared for craniotomy surgery. In group 1 and 2, 1 mg/kg of dexmedetomidine and esmolol were dissolved in 10 cc normal saline, respectively, and in group 3, 50 mg/kg of magnesium sulfate was dissolved in 100 cc normal. The same drugs were given to patients as the initial or loading dose. After anesthesia and intubation, patients in group 1, 2, and 3 were given dexmedetomidine (0.5 mg/kg/h), esmolol (0.5 mg/kg/h), and magnesium sulfate (15 mg/kg/h) as an infusion.

The questionnaire was completed by all groups, in which PR, MAP (Mean Arterial Pressure), mean bleeding score, mean of received packed cells, controlled hypotension and bradycardia, and survival of patients were recorded. Toward a perfectly blinded study, all patients were unaware of the drugs they were receiving. The drugs were also prepared in all three groups by an anesthesiologist, and the initial doses were decreased to 10 cc by normal saline and given to the anesthesia resident for injection by 10 cc syringes named A, B, and C. Infusion doses were also prepared in 50 cc syringes by an anesthesiologist and named A, B, and C and given to the anesthesia resident for injection, so the anesthesia resident was also blind to type of injectable drug.

Statistical Analysis

Data were analyzed using spss software version 19, and ANOVA and T-Test were used for statistical significance analysis.

Ethical Considerations

The present study was approved by Ethics Committee of University of Medical Sciences (code of ethics: IR.ARAKMU.REC.1396.267; IRCT code: IRCT20141209020258N86). In all stages of the study, including writing a proposal, collecting samples, and analyzing the data, the researchers were required to consider ethical principles approved by the Ministry of Health and the Helsinki Declaration. This Also, no cost was imposed on the patients' family, a written consent was obtained from the subjects and they were assured that their information would be treated as strictly confidential.

Results

A total of 45 patients were entered into the study and divided into three groups: dexmedetomidine, esmolol, and magnesium sulfate. The mean age and standard deviations of the three groups of dexmedetomidine, esmolol and magnesium sulfate were 36.78±10.32, 34.47±10.58, and 39.67±11.99 years, respectively. In terms of age, there was no significant difference between the three groups (p=0.438).

The number and percentage of women in the dexmedetomidine, esmolol, and magnesium sulfate groups were 6 and 40%, 7 and 46.6%, and 7 and 46.6%, respectively. The number and percentage of men in the dexmedetomidine, esmolol, and magnesium sulfate groups were 9 and 60%, 8 and 53.4%, and 8 and 53.4%, respectively. In terms of gender, there was no significant difference between the three groups (p=0.914).

The mean and standard deviation of baseline blood pressure in dexmedetomidine, esmolol, and magnesium sulfate groups were 100.45±7.32, 99.58±7.86, and 9.87±99.82, respectively. In terms of baseline blood pressure, there was no significant difference between the three groups (p=0.932).

The mean and standard deviation of heart rate in dexmedetomidine, esmolol, and magnesium sulfate groups were 88.07±5.09, 3.94±90.60, and 90.47±4.44, respectively. In terms of heart rate, there was no significant difference between the three groups (p=0.932).

Table 1. The mean and standard deviation of heart rate

Group	Mean	SD	P value
Dexmedetomidine	88.07%	5.09	0.236
Esmolol	90.60%	3.94	
Magnesium sulfate	90.47%	4.44	

The number and percentage of GOS=4 in dexmedetomidine, esmolol, and magnesium sulfate groups were 0 and 20%, 3 and 20%, and 6 and 33.3%, respectively. The number and percentage of GOS=5 in dexmedetomidine, esmolol, and magnesium sulfate groups were 15% and 100%, 12 and 80%, and 9 and 66.7%, respectively. In terms of GOS, there was significant difference between the three groups (p=0.007).

As shown in Table 2 and Figure 1, the mean arterial pressure (15-90 minutes) in magnesium sulfate group is higher than the two other groups; however, the mean arterial pressure (120 minutes) in the esmolol group was higher than the other two groups.

Table 2. Descriptive information of MAP in the three groups

Group	15 min	30 min	45 min	60 min	90 min	120 min
Dexmedetomidine	8.13 ± 63.00	3.68 ± 62.53	3.76 ± 59.8	4.52 ± 58.47	5.03 ± 59.2	6.37 ± 61.33
Esmolol	4.61 ± 70.13	4.77 ± 67.93	4.5 ± 65.53	5.67 ± 64.13	5.23 ± 67.4	4.66 ± 69.4
Magnesium sulfate	7.37 ± 72.67	6.35 ± 68.33	7.75 ± 66.53	7.02 ± 65.2	7.3 ± 93.66	7.15 ± 69.07

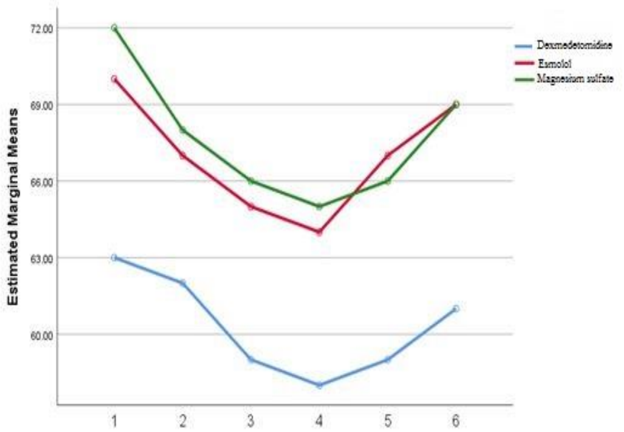

Figure 1. Data of the three groups based on MAP

Table 3 shows the Greenhouse-Geisser test results. In terms of Greenhouse-Geisser test, there is a significant difference between the three groups (P=0.05).

Table 3. Greenhouse-Geisser test results

	Total squares	Degree of freedom	F test	P value
Time	1041.51	2.57	43.86	0.0001
Group	3004.20	2	7.93	0.001
Time*group	114.56	5.13	2.41	0.04*

As shown in Table 4 and Figure 2, the mean heart rate in magnesium sulfate group (15-120 minutes) is higher than the other two groups.

Table 4. Descriptive information of heart rate in the three groups

Group	15 min	30 min	45 min	60 min	90 min	120 min
Dexmedetomidine	1.73 ± 75.53	1.96 ± 73.53	2.06 ± 71.33	1.21 ± 69.8	1.36 ± 71.47	1.24 ± 73.6
Esmolol	4.39 ± 70.53	3.88 ± 67.93	2.84 ± 66.07	3.7 ± 65.33	3.23 ± 67.47	2.96 ± 70.27
Magnesium sulfate	4.57 ± 80.80	4.56 ± 78.53	4.26 ± 76.47	3.93 ± 74.8	3.95 ± 77.07	4.61 ± 79.33

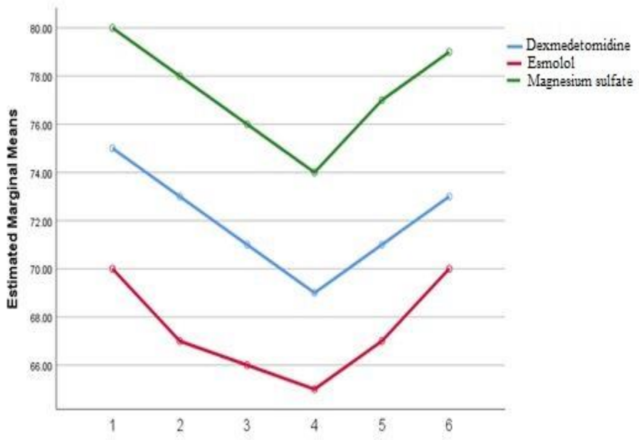

Figure 2. Data of the three groups based on heart rate

As shown Table 5, in terms of Greenhouse-Geisser test, there is no significant difference between the three groups (P>5%).

Table 5. Greenhouse-Geisser test results

	Total squares	Degree of freedom	F test	P value
Time	976.16	3.57	108.01	0.0001
Group	4417.34	2	37.06	0.0001
Time*group	29.59	7.14	1.64	0.128

As shown in Table 6, in terms of generalized linear model (GLM), there is a significant difference between the three groups (P<0.05).

Table 6. Generalized linear model results

	Wald chi square	Degree of freedom	P-value
Time	5521.6	2	0.0001
Group	6.01	1	0.05
Time*Group	29.88	8	0.0001*

Discussion

Controlling hemodynamic parameters and creating stability along with reducing bleeding during surgery are the pillars of anesthesia management, which in addition to decreasing cardiovascular complications after surgery, reduces the risk of blood transfusions and related complications such as hemolysis, infection, non-hemolytic transfusion reactions, and pulmonary complications. Therefore, it is important to achieve a specific drug or drug combination to effectively control blood pressure in craniotomy surgery, which is safe for the heart, provides good hemodynamics, with fewer side effects (Srebro et al., 2017).

In the present study, the mean age and standard deviation in the three groups of dexomidine, esmolol and magnesium sulfate were 10.32% (36.78, 10.58) ± (34.37 and 11.99), respectively (39.67%).

In the present study, the mean age and standard deviation of the three groups of dexmedetomidine, esmolol and magnesium sulfate were 36.78±10.32, 34.47±10.58, and 39.67±11.99 years, respectively, which were not significant (p=0.438).

In addition, the number and percentage of women in the dexmedetomidine, esmolol, and magnesium sulfate groups were 6 and 40%, 7 and 46.6%, and, 7 and 46.6%, respectively. Also, the number and percentage of men in the dexmedetomidine, esmolol, and magnesium sulfate groups were 9 and 60%, 8 and 53.4%, and 8 and 53.4%, respectively. In terms of gender, there was no significant difference between the three groups (p=0.914).

In the present study, in terms of heart rate, there was a significant different between the groups without considering the time variable (p= 0.0001); however, considering the time variable, no significant difference was observed (p=0.128). This means that, in spite of their reduction power, none of the drugs could change significantly and effectively the heart rate over time. This was consistent with the study by Ovais Nazi et al (2016), in which the mean heart rate during surgery in the dexmedetomidine group (56.1) was significantly lower than the esmolol group (Nazir et al., 2016). Nevertheless, similar to our study, the MAP during surgery in the dexmedetomidine and esmolol groups was 60.2 and 68.875, respectively (P = 0.02).

In our study, patients had the GOS score of 4 and 5, and no lower score were observed. The number and percentage of GOS=4 in dexmedetomidine, esmolol, and magnesium sulfate groups were 0 and 20%, 3 and 20%, and 6 and 33.3%, respectively. The number and percentage of GOS=5 in dexmedetomidine, esmolol, and magnesium sulfate groups were 15% and 100%, 12 and 80%, and 9 and 66.7%, respectively. In terms of GOS, there was significant difference between the three groups (p=0.007). This indicates that the use of dexmedetomidine has not been associated with a decrease in GOS score, and the use of this drug has reduced the GOS by 1 score. This is consistent with the results of a study by Mahajan et al. (2018). After the intervention, they found that GOS was well reported in all patients, and that the use of dexmedetomidine injection with the scalp block was safe in patients undergoing awake craniotomy (Mahajan et al., 2018).

In the present study, the MAP of dexmedetomidine group was significantly lower than the other two groups. This was consistent with a study by Vinit et al. (2016), in which blood pressure of magnesium sulfate group at different minutes of surgery was significantly lower than the control group (p=0.001) (Srivastava et al., 2016). In addition, the results of our study were consistent with a study by Khalifa OS et al. (2015), in which dexmedetomidine group had significantly the lowest MAP in surgery (60 per minute) (Khalifa and Awad, 2015).
In the present study, the bleeding score was significantly different between the three groups and significantly lower in the dexmedetomidine group than in the other two groups. This was consistent with the results of other studies: the lower the heart rate, the better the blood pressure. In a study by Ovais Nazir (2016), blood loss in the dexmedetomidine and esmolol groups was 277.8 and 308.33, respectively, which was consistent with our study (Nazir et al., 2016).

Conclusion

Comparison of the three groups in controlled hypotension in craniotomy surgery showed that the MAP and bleeding score of dexmedetomidine group was significantly lower than the other two groups, and the GOS didn’t decrease in this group. In general, dexmedetomidine would be a better choice for controlled hypotension in craniotomy.

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