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Comparison of Aprotinin and Controlled Hypotension on Blood Loss in the Herniated Intervertebral Disc Surgery

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Background: Methods of reducing blood loss in surgical procedures such as spinal disc herniation, which are characterized by severe bleeding, can reduce the need for blood transfusion and thereby the risk of infectious diseases transmission, transfusion reactions, acute lung injury, graft-versus-host disease (GVHD), hypothermia, coagulation disorders and metabolic complications. Anti-fibrinolytic drugs (e.g. Aprotinin, aminocaproic acid, desmopressin and tranexamic acid) and controlled hypotension (monitored reduction by medication) are among these methods.

Objectives: In our clinical trial, two methods of aprotinin and controlled hypotension are compared in terms of their efficacy in reducing blood loss.

Patients and Methods: 70 patients undergoing spinal disc herniation were randomly divided into two groups of controlled hypotension (treated with nitroglycerin: starting with 5 μg/minute to reach an MAP of 55 - 60 mmHg, with an increase of 5 μg/minute of the drug in every 3 - 5 minutes) and aprotinin (0.5 million units injection before surgery). The anesthesia was administered similarly to both groups and blood pressure and heart rate were recorded every 5 to 15 minutes. Moreover, the amount of bleeding and the surgeon satisfaction were measured.

Results: 70 patients were identical in terms of demographics and the length of surgery. The two groups were not statistically different in terms of mean change in systolic, diastolic and mean blood pressure and heart rate at different times. The severity of blood loss measured on Boezarrt scale for low, medium and severe bleeding was respectively 21 (30%), 27 (39%), and 12 (31%). The extent of surgeon satisfaction with the operation room measured on a 3-point Likert scale (poor, medium and good) was 18 (26%), 40 (57%), and 12 (17%), respectively. The results were almost corresponding in both groups. Also, the two groups were identical in terms of calculated blood loss and the need for additional intraoperative medication.

Conclusions: In intervertebral herniated disc surgery, aprotinin and controlled hypotension treatments yielded similar results in terms of reducing blood loss and surgeon satisfaction with the field of operation.

Keywords: Orthopedics; Hypotension; Controlled; Aprotinin

1. Background

There are variety of methods to reduce the blood loss in surgeries, especially those characterized with severe bleeding such as spine surgery. With reduced surgical bleeding, the results of operations can be improved by developing an appropriate operation field. Also, given the decreased need for blood transfusion, the patients are largely protected against blood transfusion risks and indiscriminate consumption of blood products (1-3).

Blood transfusion is characterized by serious complications such as the transfer of infectious diseases, transfusion reactions, acute lung injury, graft-versus-host disease, hypothermia, coagulation disorders, and metabolic consequences, which can be largely prevented by reducing the need for blood transfusion (4-6).

Moreover, Besides is spoken, bleeding has detrimental effects on cardiovascular, pulmonary, renal and hepatic apparatus, the intensity of which is directly related to the severity of the blood loss (7). In recent years, enormous efforts have been made to prevent or treat bleeding complications, which have ultimately led to reduced need for blood and blood products.

One of the common methods for reducing the prescription of blood products is the use of anti-fibrinolytic drugs (8). With extensive studies on the pathophysiology of postoperative bleeding and greater insights about the mechanisms of fibrinolytic, many studies were carried out on the application of anti-fibrinolytic drugs in 1990s, thereby preparing the ground for the introduction of more effective drugs such as Aprotinin, aminocaproic acid, desmopressin, and tranexamic acid

that could reduce blood loss and the need for allogeneic transfusions (9).

As an anti-fibrinolytic drug, aprotinin is a nonspecific protease serine inhibitor drug that reduces postoperative bleeding through a variety of mechanisms. It inhibits proteases involved in coagulation, fibrinolytic and complement cascade.

Moreover, it retains lb receptors at the level of platelet along with anti-inflammatory effects like corticosteroids that thwart the release of tumor necrosis factor caused by external circulation (10).

Controlled hypotension or monitored reduction of blood pressure by medication is another method commonly used to lessen the amount of blood loss. Different drugs are used to reduce controlled blood pressure including vasodilators (nitroprusside, nicardipine), alpha agonists (clonidine, dexmedetomidine) beta-adrenoceptor antagonists (Inderal, Esmolol) and alpha and beta antagonist (Labetalol) (11-13). Many studies have confirmed the efficacy of controlled hypertension on reducing blood supply during surgery by restricting the blood supply to the surgical site.

2. Objectives

This study is an attempt to compare these two methods in terms of blood loss reduction.

3. Patients and Methods

This study was a prospective interventional clinical trial administered to 70 patients admitted to a general hospital in the city of Mashhad for intervertebral herniated disc surgery. All patients, aged 18 to 60 years, were graded in ASA Class I and II without any pathology of the cardiovascular system, heart failure, hypertension, liver or kidney disease, blood system pathology, hemoglobin below 10, coagulation disorders, or consumption of aspirin and hemorrhagic medications. Before surgery, all patients were tested for blood cell count, blood urea, serum creatinine, and prothrombin. The evaluations were made only by one surgeon. The inclusion criteria were: admission for intervertebral herniated disc surgery, non-emergency nature of the surgery, initial hemoglobin level ranging from 10 to 12. The exclusion criteria included any unexpected factor that could complicate or prolong the surgery, patients suffering from multiple trauma or hypertension, reoperation, diseases leading to clotting disorder or coagulopathy and patients prohibited from the intake of aprotinin and the length of operation less than 3 hours.

The study variables were as follow: systolic and diastolic blood pressure, heart rate before and after intubation and during the operation, blood loss, and surgical site quality, and surgeon satisfaction with the surgery. In keeping with the objectives of the study and the results of previous research conducted with the same method, a sample size of 35 subjects was estimated for each group using simple randomized sampling method. Among all patients undergoing intervertebral herniated disc surgery in Imam Reza Hospital in Mashhad, those signing an informed consent for participation in the study were selected. Then, the patients were randomly divided in two groups where controlled hypotension was induced by nitroglycerin in one group and aprotinin was given to the second group. Nitroglycerin doses were initially added at a rate of 5 mg/minute and every three to five minutes another 5 mg was added to achieve the favorable impact (Systolic blood pressure below 70 to 80 and 55 to 60 mmHg MAP). Max dose of TNG was 20 mg/minute. In Aprotinin group, 0.5 million units were administered to the patient before surgery.

After positioning patients on the operating table and following the preparation and pre-oxygenation of the patient, the 0.05 mg/kg midazolam, 1 mg/kg fentanyl and 1 mg/kg lidocaine were administered as the pre-medication. Then, 5 mg/kg induced thiopental and 5 mg/kg atracurium were injected and the patients were intubated by an endotracheal tube of the right size after 5 minutes. The propofol infusion (100 μg/g/min) was administered to maintain the anesthesia. 10 mg atracurium was injected every 30 minute and the systolic and diastolic blood pressures and heart rate were measured after putting the patient on the operating table and performing the intubation by a noninvasive method.

During the surgery, the arterial blood pressure and heart rate of the patient were measured and recorded every 5 minutes for 15 minutes, a process that was repeated every 15 minutes. The electrical activity of the heart and end-exhalation carbon dioxide measurements was also monitored. To measure the blood loss, the number of gauzes, the amount of blood in the suction and surgeon satisfaction with the operation site was considered. Moreover, Boezarrt (Table 1) and Likert scales were used to quantitatively evaluate the surgeon satisfaction. The length of operation was calculated from the injection of anesthetic until the end of operation. 15 minutes before the operation and after consultation with the surgeon, the patient's anesthesia was lessened and following the full muscle strength recovery achieved after the reverse injection, the patient was extubated and transferred to the recovery room only to be moved to the ward upon obtaining the discharge criteria.

The SPSS software v.16 was sued for data analysis. The descriptive analysis was presented by tables and diagrams and analytical analysis was carried out by comparative tests (t-test, chi-square and repeated measurement test) between the two groups at the significance level of 0.05.

4. Results

Given the normal distribution of all variables in the study, parametric statistical tests were used for data analysis. According to the results, the age of patients was between 20 and 60 years with a mean age of 40.56 ± 13.23 years. The mean age of aprotinin and controlled hypo-

tension groups was 42.57 ± 12.89 and 38.54 ± 13.45 years, respectively. The results of t-test did not show any significant differences between the two groups in terms of age distribution (P = 0.205).

The results of Chi-squared test showed that two groups were not significantly different in terms of gender (P = 0.8) (Table 2). Also, the t-test indicated that the participants were relatively homogenous in terms of weight (P = 0.980).

As shown by the statistical results, the mean length of surgery was 110.36 ± 26.95 minutes for all patients. The mean length of surgery was 111.71 ± 25.69 for the aprotinin group and 100.00 ± 28.46 for the controlled hypotension group respectively. The results of t-test did not show any significant difference between the two groups with respect to the length of surgery (P = 0.677).

The mean systolic blood pressure showed a decline in both groups compared to the baseline. According to results of repeated measurement test, this reduction was significantly different from the baseline throughout the study (P < 0.0001). In the aprotinin group, the systolic blood pressure changes were not significantly different during the study. The mean systolic blood pressure was 136.91 ± 17.75 in the controlled hypotension and 120.89 ± 15.95 in the aprotinin group at the baseline and 115.89 ± 21.163 for the controlled hypotension and 116.61 ± 13.62 for the aprotinin group at the end of study (Figure 1).

The mean systolic blood pressure at different times was not statistically significant between the two groups (P = 0.3). Compared to the baseline, the mean diastolic blood pressure demonstrated a reduction in both groups throughout the study. According to the results of repeated measurement test, this reduction was significantly different from the baseline in the controlled hypotension group (P < 0.0001). In the aprotinin group, the diastolic blood pressure variations were not significantly different during the study period (P = 0.06).

The mean diastolic blood pressure was 82.54 ± 9.40 in the controlled hypotension and 78.17 ± 9.9 in the Aprotinin group at the baseline and 78.17 ± 9.93 for the controlled hypotension and 73.80 ± 10.32 for the aprotinin group at the end of study (Figure 2). The mean diastolic blood pressure at different times was not statistically significant between the two groups (P = 0.71).

Table 1. Level of Surgeon Satisfaction Based on Boezarrt Scale

Score	Evaluation of the Severity of Bleeding Based on Boezarrt Scale
0	Without bleeding (conditions corresponding to that of a corpse)
1	Minor bleeding (no need for suction)
2	Slight bleeding (occasional suction)
3	Low bleeding (regular suction, the field is filled with blood a few seconds after removing suction)
4	Moderate bleeding (regular suction, the field is filled with blood immediately after removing suction)

Table 2. Gender of Participants [a]

Gender	Aprotinin	Controlled Hypotension	Total	P
Male	17 (49.6)	5.3	36 (100)	0.8
Female	18 (51.4)	45.7	34 (100)	0.8

[a] Values are presented as frequency (percentage).

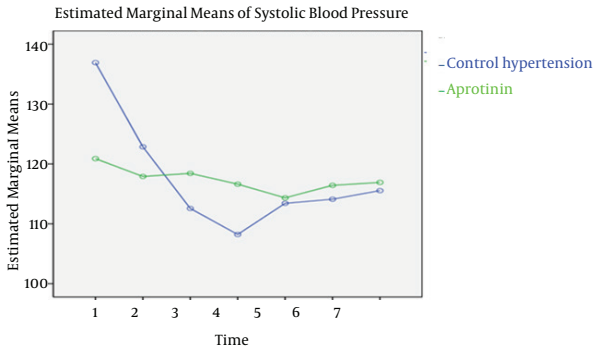

Figure 1. Comparison of Systollic Blood Pressure Variation at Different Times in Aprotinin and Controlled Hypotension Groups

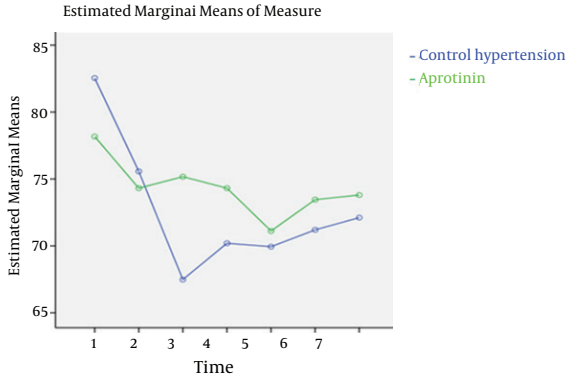

Figure 2. Comparison of Diastolic Blood Pressure Variation at Different Times in Aprotinin and Controlled Hypotension Groups

During the study period, the mean blood pressure dropped in both groups compared to the baseline. According to the results of repeated measurement test, this decline was significantly different from the baseline in the controlled hypotension group ($P < 0.006$). In the aprotinin group, the mean blood pressure changes were significantly different throughout the study period ($P = 0.01$).

The mean blood pressure was 92.41 ± 10.65 in the controlled hypotension and 100.67 ± 11.36 in the aprotinin group at the baseline and 88.17 ± 12.88 for the controlled hypotension and 86.59 ± 15.03 for aprotinin group at the end of study. The mean blood pressure was not statistically significant between the two groups at different times ($P = 0.47$).

The mean heart rate showed a decline in both groups compared to the baseline. According to the results of repeated measurement test, this reduction was significantly different from the baseline in the controlled hypotension and aprotinin groups throughout the study period ($P = 0.0001$).

The mean heart rate was 83.64 ± 11.50 in the controlled hypotension and 81.15 ± 13.60 in the aprotinin group at the baseline and 69.02 ± 13.44 for the controlled hypotension and 70.54 ± 15.18 for the aprotinin group at the end of study. The mean heart rate was not statistically significant between the two groups ($P = 0.47$).

The analysis of bleeding severity based on Boezarrt scale (measured by chi-square test) did not show any significant difference between the two groups ($P = 0.413$) (Table 3).

According to the results, the estimated blood loss during surgery was 518.00 ± 118.82 cc for all patients. This figure was 516.86 ± 114.37 for the aprotinin group and 519.14 ± 124.77 cc for controlled hypotension group.

The results of t-test did not show any significant difference between the two groups in terms of blood loss during surgery ($P = 0.937$).

The level of surgeon satisfaction with operating room was measured on a 3-point Likert scale as poor 18 (26%), medium 40 (57%) and good 12 (17%). The chi-square test did not show any significant difference between the two groups in this respect ($P = 0.346$).

In total, 14 (20%) of the patients required medications out of which 10 (28%) patients belonged to the aprotinin group and 4 patients (11%) to the controlled hypotension groups. Again, the results of chi-square test did not indicate any significant differences between the two groups in terms of the need for additional medications ($P = 0.073$).

5. Discussion

The results of the present study revealed that two groups were not statistically different in terms of mean change in systolic and diastolic blood pressure and mean heart rate at different times. The severity of bleeding and surgeon satisfaction was identical in both groups. Moreover, the estimated blood loss and the need for additional medication during surgery were also corresponding in both groups.

This is consistent with the results of similar studies about the effect of antifibrinolytic aprotinin and tranexamic acid on reducing blood loss during the orthopedic and other surgeries (8, 14, 15, 16). A study by van der Linden et al. (2005) examined the effect of aprotinin and placebo in reducing the blood loss and the need for transfusion in patients who had undergone open-heart surgery and used Plavix drug. The results indicated that aprotinin could significantly reduce the blood transfusion and bleeding in these patients (15).

A similar study by Lindvall et al. (2005) investigated the blood loss after emergency open-heart surgery, concluding that the administration of aprotinin reduced the need for blood transfusions and platelet, lessening the intraoperative bleeding and overall bleeding in patients (16). Their results were consistent with the findings of the present study.

Okubadejo et al. (2007) also examined the effect of aprotinin administration in bleeding reduction during surgery in Spain. They carried out a cohort study on 80 patients in two groups to investigate the blood loss, the need for blood products and other complications in these groups. The results suggested that aprotinin reduced blood loss in surgery, but at the same time increased the risk of kidney damage in women over 60 (17).

In a similar study, Tayyab et al. (2008) examined the effect of aprotinin on reducing blood loss in spinal deformity correction surgery in 82 patients, concluding that it reduced blood loss and the need for blood transfusion (18). Given the resemblance between our study and that of Tayyab et al. (18) it can be concluded that aprotinin or controlled hypotension are effective in bleeding reduction in spinal surgeries.

Table 3. Blood Loss Based on Boezarrt Scale for All Patients in Aprotinin and Controlled Hypotension Groups [a]

	Bleeding Based on Boezarrt Scale			
	Aprotinin	**Controlled Hypotension**	**Total**	**P**
Low bleeding	13 (37)	20 (23)	21 (30)	0.413
Medium bleeding	17 (48)	57 (57)	27 (39)	0.413
Severe bleeding	5 (14)	7 (20)	21 (31)	0.413

[a] Values are presented as frequency (percentage).

Bai et al. (2008) investigated the severity of blood loss in neurosurgeries in three groups (control group, hemodilution with controlled hypotension and hemodilution with aprotinin), finding that despite reduced intraoperative bleeding, there was not any significant difference between the two groups (19). In spite of the difference in surgical procedure and the use of hemodilution, the efficacy of aprotinin and controlled hypotension in reducing bleeding was corresponding to our study.

In line with the results of this research, a study by Pleym et al. (20) in 2003 and a meta-analysis (21) in 2012 revealed that antifibrinolytic drugs such as aprotinin were effective in bleeding reduction during surgery.

According to the findings of this study and consistent with the literature, it can be concluded that in intervertebral spinal herniated disc surgery, controlled hypotension and aprotinin can reduce blood loss and increase the surgeon satisfaction with the field of operation.

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Authors' Contributions

Mehdi Fathi, and Saeid Jahanbakhsh design of the project, doing and supervision of the study. Azra Izanloo, Marjan Joudi, Mehdi Fathi, and Hosein Saadatfar writing the manuscript, and analysis and interpretation of data. Hosein Saadatfar, F. Azam Lotfi, Alireza Bameshki, Mahyar Taghavi, and Azam Sabri design of the project, doing the study, and acquisition of data.

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