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Deneysel Çalışma

Comparison of permissive hypotensive resuscitation, low-volume fluid resuscitation, and aggressive fluid resuscitation therapy approaches in an experimental uncontrolled hemorrhagic shock model

Deneysel kontrolsüz hemorajik şok modelinde ılımlı hipotansif resüsitasyonu, düşük volümlü sıvı resüsitasyonu ve agresif sıvı resüsitasyonu tedavi yaklaşımlarının karşılaştırılması

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BACKGROUND
In this study, we aimed to compare the efficacy of aggressive fluid resuscitation, low-volume fluid resuscitation and permissive hypotensive resuscitation in an experimental uncontrolled hemorrhagic shock model.

METHODS
Forty-four male Guinea pigs were used in the study in an experimental uncontrolled shock model. Guinea pigs were split into six groups including normovolemic-normotensive fluid treatment group, normovolemic-permissive hypotensive fluid treatment group, low-volume normotensive fluid treatment group, low-volume permissive hypotensive fluid treatment group, no treatment (n=6), and sham-operated groups (n=6). Resuscitation was initiated when mean arterial pressure (MAP) reached 30 mmHg. In the permissive hypotensive resuscitation group, fluid treatment continued until MAP reached 45±5 mmHg and in the aggressive fluid groups until MAP reached 60±5 mmHg. Resuscitation fluid was hetastarch 6% (hydroxyethyl starch) in the low-volume fluid groups and Ringer's lactate in the normovolemic fluid groups.

RESULTS
Mean survival time was 122.75±4.83 min in the normovolemic-normotensive fluid group, 130.87±16.31 min in the normovolemic-permissive hypotensive group, 122.12±11.53 min in the low-volume-normotensive fluid group, and 152.25±9.10 min in the low-volume-permissive hypotensive fluid group. Survival time was found significantly higher in the group in which low-volume-permissive hypotensive fluid treatment was applied than in the other groups.

CONCLUSION
When pressure effect was compared during treatment, permissive-hypotensive resuscitation was found more effective in both groups that received colloid and crystalloid treatment.

Key Words: Guinea pigs; hemorrhage; resuscitation; shock.

AMAÇ
Bu çalışmada, deneysel kontrolsüz hemorajik şok modelinde agresif sıvı resüsitasyonu, düşük volümlü sıvı resüsitasyonu ve ılımlı hipotansif resüsitasyonun etkinliği karşılaştırıldı.

GEREÇ VE YÖNTEM
Çalışmada 44 erkek Guinea pig türü kobay kullanıldı. Deneysel kontrolsüz hemorajik şok modeli uygulandı. Kobaylar normovolemik-normotansif sıvı tedavisi alan grup, normovolemik-ılımlı hipotansif sıvı tedavisi alan grup, düşük volümlü-normotansif sıvı tedavisi alan grup, düşük volumlü-ılımlı hipotansif sıvı tedavisi alan grup, tedavi almayan grup (n=6) ve kontrol grubu (n=6) olmak üzere altı gruba ayrıldı. Ortalama arter basıncı (OAB) 30 mmHg olduğunda resüsitasyona başlandı. Ilımlı hipotansif resüsitasyon gruplarında OAB 45±5 mmHg olacak şekilde ve agresif resüsitasyon gruplarında OAB 60±5mmHg olacak şekilde sıvı uygulandı. Düşük volümlü sıvı tedavisi alan gruplarda hetastarch 6% (hidroksietil nişasta) ve normovolemik sıvı tedavisi alan gruplarda Ringer laktat kullanıldı.

BULGULAR
Ortalama yaşam süresi normovolemik-normotansif grupta 122,75±4,83 dk, normovelemik-ılımlı hipotansif grupta 130,87±16,31 dk, düşük volümlü-normotansif grupta 122,12±11,53 dk, düşük volümlü-ılımlı hipotansif grupta 152,25±9,10 dk idi. Düşük volümlü ılımlı hipotansif grupta yaşam süresi diğer gruplardan istatistiksel olarak anlamlı düzeyde yüksek bulundu.

SONUÇ
Normotansif gruplarda kolloid ve kristalloid etkinliği benzer olmasına rağmen ılımlı hipotansif gruplarda kolloid tedavisi daha etkili bulundu. Sıvı tedavisine basıncın etkisi karşılaşıtırıldığında ılımlı hipotansif resüsitasyonun, kolloid ve kristalloid kullanılan grupların tamamında daha etkili olduğu bulundu.

Anahtar Sözcükler: Kobay; hemoraji; resüsitasyon; şok.

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Trauma is the number one cause of death under 40 years of age.[1] Uncontrollable hemorrhage and shock are responsible for 40% of deaths from trauma.[2] New methods have replaced the conventional methods of shock resuscitation. The current therapy for hemorrhagic shock aims at rapid and aggressive fluid resuscitation and provides normal blood pressure level and sufficient tissue perfusion.[3-6]

Monitoring of shock is based on vital findings, urinary output, cardiac output, and indirect markers of cellular perfusion.[7,8] Even if these parameters can be improved rapidly, complications and associated mortality may occur in the late stage of the shock. In recent reports, rapid and aggressive fluid therapy before control of surgical hemorrhage in trauma cases has been shown to cause complications such as dilutional coagulopathy, increase in the hemorrhage volume, increased acidosis, and hypothermia, as well as increase in mortality.[7,9-15] Pulmonary and brain edema, gastrointestinal ischemia and massive ischemic edema due to increased intravascular fluid volume have been reported among the complications of aggressive fluid therapy.[16,17]

Experimental studies on hemorrhagic shock have shown that limited fluid therapy positively contributes to survival.[10,15,18,19] Low-volume fluid resuscitation refers to use of fluids like colloids at low volumes but high oncotic pressure. Permissive hypotensive resuscitation, however, refers to fluid therapy at pressures that will provide perfusion of vital organs.[20] This method aims at supporting hemostasis and preventing hemodilution at low blood pressure levels, thus maintaining a high density of cellular components (red blood cells) that act as a transporter in carrying oxygen to the tissues.[19]

This study aimed to compare the efficiency of aggressive fluid resuscitation with low-volume fluid resuscitation and permissive hypotensive resuscitation therapy approaches in an experimental uncontrolled hemorrhagic shock model.

MATERIALS AND METHODS

The study protocol was approved by the Animal Experimentation Ethics Committee, Gülhane Medical Academy. The study subjects included 44 male Guinea pigs weighing 500-700 g, divided into 6 groups as:

– Control group (Group 1, n=6);

– No treatment group (Group 2, n=6);

– Normovolemic normotensive fluid therapy group (Group 3, n=8);

– Normovolemic permissive hypotensive fluid therapy group (Group 4, n=8);

– Low-volume normotensive fluid therapy group (Group 5, n=8);

– Low-volume permissive hypotensive fluid therapy group (Group 6, n=8).

The animals were kept nil per os for 12 hours before the study. All the animals were sedated with xylazine 3-5 mg/kg (Alfazyne 2% injectable, EgeVet, Izmir, Turkey) and ketamine 20-40 mg/kg (Alfamine 10% injectable, EgeVet, Izmir, Turkey). Additional doses were administered if necessary. For fluid infusion, the left jugular vein was catheterized with a 26-gauge intra-cath (MEDIFLON™). For constant pressure monitoring and blood sampling, the right carotid artery was catheterized with a 26-gauge intra-cath (MEDIFLON™). The animals were placed in supine position and after sterilization of the abdominal wall, the abdomen was entered via a left subcostal incision. A parenchymal incision was made in the transverse direction at two levels between the three main branches of the splenic artery. After allowing the free flow of the blood into the peritoneal cavity, the abdominal incision was closed. In the control group, only laparotomy was performed and then the incision was closed. Resuscitation was not started until the mean arterial pressure (MAP) reached 30 mmHg.

In the normotensive resuscitation groups, normal MAP values (65±5 mmHg) for Guinea pig species were obtained by fluid infusion.[21] Similarly, in the groups that underwent permissive hypotensive resuscitation, a MAP value of 45±5 mmHg was achieved with fluid infusion. Resuscitation was done with 6% HES (hydroxyethyl starch) in the groups that received low-volume fluid therapy and with Ringer's lactate solution in the groups that received non-volemic fluid therapy. For constant pressure monitoring, a pressure monitor set (Bıçakçılar®, Istanbul, Turkey) and Cardiocap/5 monitor (Datex-Ohmeda®, Louisville, CO, USA) were used. The study was ended when the animals developed respiratory arrest or when MAP values decreased below 20 mmHg despite fluid infusion. The survival time of the animals was recorded. To monitor hematocrit values and serum lactate levels of the animals, blood samples of the animals were obtained at 0 and 60 minutes (min.) and every 30 mins. subsequently. Serum lactate levels were measured with Kodak EKTACHEM DT60 II System (Johnson&Johnson®, Rochester, New York, USA). After resuscitation was ended, the peritoneal cavity was opened and the amount of blood loss was measured by withdrawing the blood into an injector. The data for each group were statistically evaluated and compared.

Statistical evaluation was carried out using SPSS for Windows 11.0. Kruskal-Wallis test was used for constant variables in intergroup comparisons, and Bonferroni-adjusted Mann-Whitney U test was used in the paired comparisons of the groups. A value of $p \leq 0.05$ was considered statistically significant.

RESULTS

Mean survival times, amount and rate of hemorrhage and amounts and rate of infused volumes of the groups are summarized in Table 1.

Survival Time

A comparison of Group 2 with the other groups showed that treatment groups had statistically significantly longer survival (Table 2). Only the survival time of Group 6 was statistically significantly longer than in the other groups (Table 2). A comparison of the groups for the effect of the fluid volume infused on the survival time based on these data showed that the survival times of the groups that received fluid therapy at normotensive pressures (Groups 3 and 5), low-volume fluid therapy, and normovolemic fluid therapy were similar (p=1). However, in the comparison of permissive hypotensive therapy groups (Groups 4 and 6), the survival time was statistically significantly longer in Group 6 (p=0.036).

When the groups that received normovolemic fluid therapy (Groups 3 and 4) were compared for the effect of blood pressure on the survival time, Group 4 had longer survival time, but the difference was not statistically significant (p=0.052). However, the comparison of low-volume fluid therapy groups (Groups 5 and 6) showed that Group 6 had statistically significantly longer survival time (p=0.006). The data obtained in the paired comparisons of the groups are provided in Table 2.

The Amount and Rate of Hemorrhage

The mean amounts and rates of hemorrhage for all groups are summarized in Table 1. Paired comparisons of Group 2 with the other groups revealed that the treatment groups had significantly higher amount of hemorrhage ($p<0.05$). In the paired comparisons of the therapy groups, Group 4 had a significantly lower amount of hemorrhage than the other treatment groups (Table 3). While Group 6 had the highest amount of hemorrhage, the difference was not statistically significant ($p<0.05$).

When the groups that received normotensive fluid therapy (Groups 3 and 5) were compared for the effect of fluid volume infused on the amount of hemorrhage, the amounts of hemorrhage were similar (p=1). The comparison of the permissive hypotensive fluid

Table 1. Mean survival times, amount and rate of hemorrhage and amounts and rate of infused volumes of the groups

Group	Survival time (min) (Mean±SD)	Amount of hemorrhage (ml) (Mean±SD)	Rate of hemorrhage (ml/kg/h) (Mean±SD)	Infused volume (ml) (Mean±SD)	Infusion rate (ml/kg/h) (Mean±SD)
Group 1	–	–	–	–	–
Group 2	97.83±9.60	26±1.41	26.95±3.24	–	–
Group 3	122.75±4.83	40.25±3.37	33.05±1.93	55±7.15	45.05±8.06
Group 4	130.87±16.31	34.37±2.39	27.31±4.25	41.25±7.14	33.02±7.97
Group 5	122.12±11.53	41.75±4.17	34.03±3.39	54.50±4	44.70±3.75
Group 6	152.25±9.10	48.62±11.38	31.78±8.5	57±5.29	37.44±5.56

Table 2. Statistical analyses of the survival time between groups

Group	Group 2	Group 3	Group 4	Group 5	Group 6
Group 2	–	**p=0.02**	**p=0.05**	**p=0.04**	**p=0.02**
Group 3	**p=0.02**	–	p=0.052	p=1	**p=0.01**
Group 4	**p=0.05**	p=0.052	–	p=1	**p=0.036**
Group 5	**p=0.04**	p=1	p=1	–	**p=0.01**
Group 6	**p=0.02**	**p=0.01**	**p=0.036**	**p=0.01**	–

Table 3. Statistical analyses of the amount of hemorrhage between groups

Group	Group 2	Group 3	Group 4	Group 5	Group 6
Group 2	–	**p=0.02**	**p=0.02**	**p=0.02**	**p=0.02**
Group 3	**p=0.02**	–	**p=0.018**	p=1	p=1
Group 4	**p=0.02**	**p=0.018**	–	**p=0.03**	**p=0.018**
Group 5	**p=0.02**	p=1	**p=0.03**	–	p=0.01
Group 6	**p=0.02**	p=1	**p=0.018**	**p=0.01**	–

Table 4. Statistical analyses of the rate of hemorrhage between groups

Group	Group 2	Group 3	Group 4	Group 5	Group 6
Group 2	–	**p=0.05**	p=1	–	p=1
Group 3	**p=0.05**	–	p=0.072	p=1	p=1
Group 4	p=1	p=0.072	–	**p=0.03**	p=1
Group 5	–	p=1	**p=0.03**	–	p=1
Group 6	p=1	p=1	p=1	p=1	–

therapy groups (Groups 4 and 6) showed that Group 6 had statistically significantly higher amounts of hemorrhage (p=0.018).

The comparisons of the groups that received normovolemic fluid therapy (Groups 3 and 4) for the effect of pressure on the amount of hemorrhage revealed that Group 4 had a significantly higher amount of hemorrhage (p=0.018). The amounts of hemorrhage in the low-volume fluid therapy groups (Groups 5 and 6) were similar (p=1).

The data obtained from the paired comparisons of the groups for the rate of hemorrhage are shown in Table 4. When the groups that received normotensive fluid therapy (Groups 3 and 5) were compared for the effect of volume on the rate of hemorrhage, Group 5 had a lower rate of hemorrhage, while a comparison of the permissive hypotensive fluid therapy groups (Groups 4 and 6) revealed that Group 6 had a lower rate of hemorrhage. However, the difference between each pair of these treatment groups was not statistically significant (Table 4).

Comparisons of the groups for the effect of pressure on the rate of hemorrhage indicated that among the normovolemic fluid therapy groups (Groups 3 and 4), Group 4 had a lower rate of hemorrhage. In the comparisons of low-volume fluid therapy groups (Groups 5 and 6), Group 6 had a lower rate of hemorrhage, but the differences were not statistically significant (p=0.05).

Hematocrit Levels

The mean hematocrit counts of the groups at 0, 60, 90, 120 and 150 mins. are shown in Table 5. The hematocrit rates of the groups at 0 min. were similar (p=1). In Group 1, the hematocrit level was constant. In the other groups, however, it had a tendency to decline (Fig. 1).

The paired comparisons of the hematocrit level of Group 1 at the 60th min. with the other groups revealed that the groups that received therapy had statistically significantly lower levels (p=0.02, p=0.02, p=0.02, and p=0.02, respectively). The paired comparisons of the hematocrit level of Group 2 at the 90th min. with the levels of the other groups showed that therapy groups had significantly lower hematocrit levels (p=0.03, p=0.03, p=0.03, respectively). No statistically significant differences were determined between

Table 5. Hematocrit levels of the groups

Hematocrit	0 min (mean%±SD)	60 min (mean%±SD)	90 min (mean%±SD)	120 min (mean%±SD)	150 min (mean%±SD)
Group 1	39.67±3.01	39.17±2.79	39.83±2.93	39.17±2.93	–
Group 2	41.67±3.14	30.68±5.81	25.40±4.83	–	–
Group 3	41.12±3.04	22.75±7.25	9.37±2.87	4.14±1.95	–
Group 4	37.87±3.80	21.79±4.77	10±2.07	4±2.16	1
Group 5	38.25±3.37	19.75±4.46	8.37±3.70	4±0.89	3±1.22
Group 6	39.50±3.74	22.50±3.74	11.25±3.70	6.25±2.05	–

Table 6. Serum lactate levels of the groups

Hematocrit	0 min (mean%±SD)	60 min (mean%±SD)	90 min (mean%±SD)	120 min (mean%±SD)	150 min (mean%±SD)
Group 1	3.1±0.24	3.21±0.57	3.3±0.24	3.36±0.25	–
Group 2	4.38±0.39	4.75±0.53	6.33±0.61	–	–
Group 3	3.25±0.33	3.89±0.46	6.61±0.36	8.17±0.43	–
Group 4	4.2±0.42	5.36±0.78	7.4±0.62	9.33±0.45	13.9
Group 5	4.08±0.2	5.58±0.36	7.48±0.32	9.53±0.3	11.1±0.29
Group 6	4.31±0.48	5.26±0.46	7.57±0.33	9.49±0.29	–

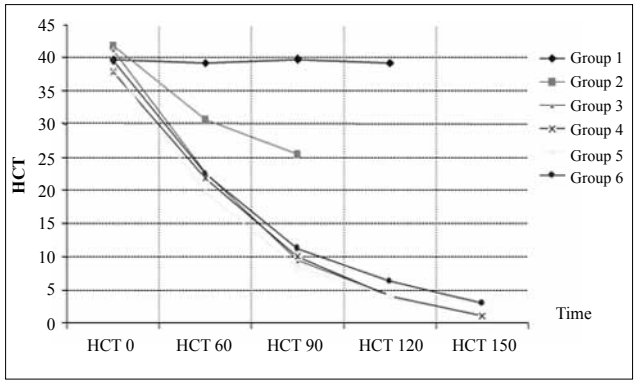

Fig. 1. Decrease in hematocrit levels over time according to groups.

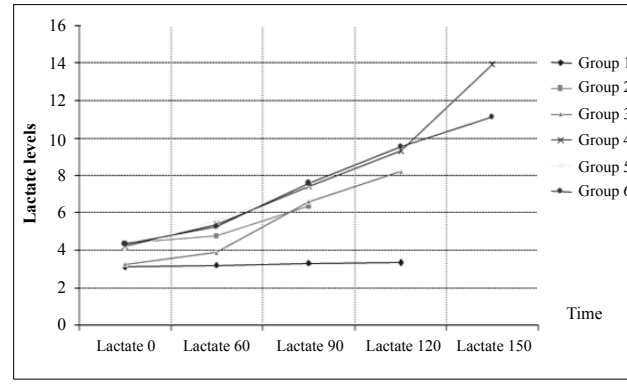

Fig. 2. Increase in serum lactate levels over time according to groups.

the therapy groups with respect to hematocrit levels at the 60th, 90th, and 120th mins. (p=0.483, p=0.342, p=0.119, respectively).

Serum Lactate Levels

The mean serum lactate levels of the groups at 0, 60, 90, 120 and 150 mins, are shown in Table 6. The serum lactate level of Group 1 remained the same; however, in the other groups, it had a tendency to increase (Fig. 2).

No statistically significant differences were detected between the serum lactate levels of the groups at 0 min. (p=0.72). The paired comparisons of Group 1 for serum lactate level at the 60th min. with the other groups showed that the serum lactate level of Group 5 was statistically significantly higher (p=0.03). However, no statistically significant differences were found between the serum lactate levels of Group 2 at 60, 90, and 120 mins. (p=0.116, p=0.314, p=0.059, respectively).

DISCUSSION

The most common cause of death associated with trauma is uncontrolled hemorrhage and shock, and 50%-80% of these deaths occur before the patients arrive at a hospital.[22] Therefore, in shock resuscitation, interventions before presentation to the hospital are important. A great proportion of the studies on reducing mortality in the early phase have focused on fluid resuscitation. Colloids, hypertonic crystalloids, and oxygen transporting fluids, which are the issues of recent debates, have intensified considerations on prevention of mortality in the early phase of traumas. Permissive hypotensive resuscitation has introduced a new approach to fluid infusion and its methods. This study aimed to compare the treatment efficiency of moderate hypotensive resuscitation and normotensive resuscitation. To this end, two types of fluids, colloid and crystalloid, and a shock model of uncontrolled hemorrhage before presentation to the hospital were used. In this model, resuscitation was started before any hemorrhage control interventions.[18,19,23-27]

In volume-controlled resuscitation models, after a hemorrhagic shock is formed, a fluid therapy is applied at a predetermined volume and rate.[23-25,27-29] In pressure-controlled resuscitation models, however, a dynamic fluid therapy is applied aiming to achieve predetermined pressure levels.[18,19,26,30,31] Volume-controlled resuscitation is more practical with respect to technique and standardization. On the other hand, pressure-controlled models have been considered more practical in clinical use.

A review of the literature for mortality rates and survival time in hemorrhagic shock models has indicated various results depending on the shock model. Mapstone et al. systematically reviewed the studies using hemorrhagic shock models and found significantly reduced mortality rates with fluid therapy in all the models.[32] The results of our study on survival time are compatible with the literature data. In only three of the studies reviewed, a splenic parenchymal incision was used as a hemorrhagic shock model. One of these studies was conducted by Solomonov et al.,[25] in which the efficiency of 41.5 ml/kg 0.9% NaCl therapy and 5 ml/kg 7.5% NaCl (hypertonic saline) therapy was compared in an uncontrolled hemorrhagic shock model. The authors found that high-volume fluid therapy statistically significantly decreased the survival time. Hatoum et al.[24] compared the efficiency of Ringer's lactate therapy with low-volume 7.5% hypertonic saline and HES therapy. In their volume-controlled fluid therapy model, high-volume Ringer's lactate therapy significantly reduced the survival time. The findings of these studies are compatible with our findings. In the study of Nan et al.,[19] a splenic parenchymal incision was performed at a single level. In this model, which was exposed to pressure-controlled fluid therapy, the effects of 0.9% NaCl infused at pressure levels of 40, 50, 60, 80, and 100 mmHg were compared; however, they did not compare the survival times. The study was designed in three phases: prehospital phase, hospital phase when hemorrhage control was achieved, and observation phase. At pressure levels of 80 mmHg

and above, they found significantly higher prehospital mortality rates. The findings of the study by Nan et al. on mortality rates are compatible with the findings of our study.

Some previous studies have reported negative effects of low-volume fluid therapy on survival time and mortality rates in volume-controlled fluid therapy models. Greene et al.[29] used a 63-rat model of 75% tail incision as a hemorrhagic shock model. In that study, volume- controlled bolus isotonic saline was infused at doses of 40 ml/kg and 80 ml/kg in 4 mins. In the group of rats that was infused with 40 ml/kg fluid, the mortality rate was significantly higher. Their findings are not consistent with our findings. This may be attributed to the negative effects on the results of their study associated with insufficient perfusion in the vital organs due to one-step bolus infusion of fluid load that was not maintained afterwards. Consequently, in uncontrolled hemorrhagic shock models, resuscitation should be uninterrupted because of ongoing hemorrhage.

In the comparisons of the groups for hemorrhage amounts, the hemorrhage amount of Group 6 was higher. In the comparisons of hemorrhage rates, however, the rates of hemorrhage in Group 4 and Group 6 were lower. This low rate of hemorrhage is considered to be parallel to the long survival time in these two groups.

Evaluation of the literature regarding the amount of hemorrhage in hemorrhagic shock models shows that all of the studies using a hemorrhagic shock model reported that moderate fluid therapy and low-volume fluid therapy reduced the amount of hemorrhage. Nevertheless, in some studies, the difference was not statistically significant. In contrast, Solomonov et al.[25] and Hatoum et al.[24] reported that high-volume fluid therapy significantly increased the amount of hemorrhage. In both studies, high-volume fluid therapy was reported to increase the mortality rate. In our study, evaluation of volume of the fluid infusion on the rate of hemorrhage indicated that low-volume fluid therapy groups had lower hemorrhage rates, although the difference was not statistically significant. Nan et al.,[19] in their pressure-controlled fluid therapy model, compared the effects of 0.9% NaCl infusion at six different pressure levels (40, 50, 60, 80, 100 mmHg). They found that at pressure levels of 80 mmHg and above, the amount of hemorrhage was significantly higher. The evaluation of the effects of pressure on hemorrhage rate revealed that in the hypotensive groups, the hemorrhage rates were lower, but the difference was not statistically significant.

In earlier studies using hemorrhagic shock models to compare hematocrit levels, no statistically significant differences were found between the treatment groups.[25,27,29-31] Nan et al.[19] found significantly low hematocrit levels at pressures of 80 mmHg and above. In our study, hematocrit levels in the normotensive fluid therapy groups were low. However, the difference was not statistically significant. This might have been associated with the massive injury model used in our study.

Serum lactate level is one of the markers in the evaluation of shock, expected mortality and response to treatment.[33-35] A review of earlier studies on serum lactate levels in hemorrhagic shock models showed that no significant differences were detected between the therapy groups in serum lactate levels, particularly in massive hemorrhage models.[19,25,28] Similarly, in our study, no statistically significant differences were found in the serum lactate levels between therapy groups. Thus, it has been reported that in studies on serum lactate levels in massive hemorrhagic shock models, measurements of serum lactate levels are not contributory. However, in controlled hemorrhagic shock models with long-term observation, measurement of serum lactate level may be useful.

Although fluid resuscitation has been known to be the primary shock treatment since the 1940s, the type of fluid that should be used is still debated.[36] The focus of debate has mostly been colloids or crystalloids. In our study, at normotensive pressures, the treatment efficiencies of colloids and crystalloids were similar with respect to survival time. However, at moderately hypertensive pressures, colloid treatment was more efficient in increasing the survival time.

Comparisons of the therapy groups for the effect of pressure demonstrated that moderately hypotensive resuscitation was more effective in the groups receiving colloid therapy than in the other treatment groups with different therapy with respect to survival time.

In conclusion, although it is not clear whether low-volume fluid therapy is superior to normovolemic fluid therapy, in this study, findings indicated positive effects of permissive hypotensive resuscitation on survival time. The data that have been accumulated to date in experimental studies need to be supported by clinical studies with large series.

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