Sodium Alginate as Treatment for Penetrating Abdominal Trauma- Feasibility Study.

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Abstract

Introduction: Penetrating abdominal injury is a major cause of death in trauma. It may cause hypovolemia leading to tissue hypoperfusion, direct organ damage and cytokine activation that cause inflammatory damage, all of which lead to death. Alginate is a natural anionic polysaccharide typically derived from brown algae. Sodium alginate hydrogel, a hemostatic agent, offers a platform for targeting both mechanical and biological injuries. The current study assessed the effect of a sodium alginate denoted VLVG (Very Low Viscosity (high) G alginate) following abdominal trauma in a swine model of penetrating abdominal injury.

Methods: Seven anesthetized pigs were instrumented with catheters and abdominal trauma was introduced by laparoscopic hepatectomy. Ten minutes after the induction of hypovolemic shock, three animals were intra-abdominally administered with VLVG and four animals with saline (controls). During 8h of continuous monitoring, various hemodynamic and biochemical variables were measured and liver biopsies for histological evaluation were taken. In order to compare the study group to the control in a specific time a-parametric Mann-Whitney test was used, assessment of tendency during time Friedman's test for a-parametric variables was used. In order to compare the effect of the treatment (i.e. normal saline VS VLVG alginate) repeated measures ANOVA model was used, and the p value was calculated based on the Greenhouse-Geiser test. This research was approved by the Hebrew University of Jerusalem ethics Committee number: MD16148533.

Results: VLVG-treated animals were more hemodynamically stable vs controls as reflected by their lower heart rate and higher blood pressure. They also had lower levels of liver enzymes and lactate and tissue damage.

Conclusions: Our results in this pilot abdominal injury model show that VLVG might be a promising new agent. The superior hemostatic and biocompatibility efficiency along with its tissue preserving properties may turn VLVG in the future to a device that could be used in the pre-hospital setting to improve survival of abdominal trauma injuries.

Introduction

Penetrating abdominal injuries is common and carries significant morbidity and mortality in war zones and in civilian setting (1–3). Abdominal organs are especially vulnerable to penetrating trauma characterized by numerous injuries to solid organs, gastrointestinal tract and vascular structures. The fatality from abdominal injuries occurs due to uncontrolled bleeding, organ damage and prolonged evacuation (4). Additionally, abdominal trauma may cause an inflammatory response that can aggravate tissue damage by causing diffuse bleeding, third space fluid loss and pancreatitis. All of these may further cause complications such as abdominal compartment syndrome, acute coronary syndrome and sepsis (4, 5). Various biomaterials for hemorrhage control have been developed in the military and civilian settings (6, 7). One of which is alginate, which is a safe, natural, biodegradable polysaccharide derived

from brown algae. Due to its low toxicity, biocompatibility and gel forming properties, alginate is used for many indications (8), including hemorrhage control. Alginate dressings maintain a physiologically moist environment that promotes tissue healing and regeneration. These non-adhesive dressings are highly absorbent and therefor are very useful to treat different wound types (9, 10). In the presence of divalent cations such as calcium ions, alginate-based biomaterial forms a hydrogel as the polymer becomes cross-linked. Therefore, alginate calcium dressings have become attractive in the biomedical field (11, 12). The use of alginate in penetrating abdominal trauma is not established yet. Taskin et al. have demonstrated the hemostatic properties of calcium alginate in experimental splenic injury model. They showed in a rat model that administration of calcium alginate gauze on an injured spleen reduced the perioperative bleeding, as reflected by hematocrit values (13).

We have previously shown in several animal models the beneficial and protective effects of specific sodium alginate composition. Briefly, we found in a murine model of extended partial hepatectomy that calcium cross linked alginate scaffolds on liver remnant, significantly improved animal survival, reduced liver inflammation and sustained hepatic synthetic function (14). We further found that low molecular weight sodium alginate denoted VLVG (Very Low Viscosity (high) G alginate) significantly reduced liver enzymes and pro-inflammatory cytokines in drug-induced liver injury model (15). In the current study we tested the effect of VLVG on hemodynamic stability and tissue damage, following abdominal trauma in swine model of penetrating abdominal injury.

Methods

Animals

Female domestic swine (45–50 kg) were used for the current study. Animals were maintained in a facility accredited by the medical school of the Hebrew University in Jerusalem. All swine were allowed to acclimate for 3 days and examined by a veterinarian to ensure good health before starting the surgery. Food was withheld the night before the experimental procedure, but free access to drinking water was provided. The joint ethics committee of the Hebrew University and Hadassah Medical Center approved the study protocol for animal welfare. The Hebrew University is an AAALAC international accredited institute. Animals were randomly assigned to experimental groups. Seven animals were included in this study, 4 in the control group that was treated with normal saline, and 3 in the study group that was treated with VLVG.

Instrumentation and monitoring

Prior to induction of anesthesia, animals were sedated with intra muscular (IM) Xylazine (1 mg/Kg, IM, Eurovet Animal Health B.V. Netherlands) and Ketamine (10 mg/Kg, IM, Vétoquinol SA France). The ear vein was cannulated for intravenous (IV) anesthesia, animals were placed in a supine position and were given a mixture of Diazepam (2 mg, IV, TEVA Pharmaceutical Industries Ltd. Israel), Ketamine (400 mg, IV), and Propofol (1–4 mg/Kg, IV, Fresenius Kabi Austria GmbH Austria), as well as Tramadol (5 mg/Kg, IM, Rafa Laboratories Ltd. Israel) for analgesia. Cefazolin (1 g, IV, Panpharma S.A. France) was given as

prophylaxis. Subsequently, animals were then intubated with a cuffed elastic endotracheal tube (7.0-mm, Portex Tracheal Tube). Anesthesia was maintained with 2% isoflurane (Piramal Critical Care Inc. PA, USA) in 100% oxygen and animals were ventilated using controlled mechanical ventilation (Datex Ohmeda SmartVent 7900, Datex-Ohmeda Inc, Madison WI USA / Narkomed 2B Anesthesia Machine - North American Drager). Tidal volume was set to 10 mL/kg with respiratory rate of 13–15 breaths per minute and inspiratory: expiratory ratio of 1:2 adjusted to reach an end-tidal PCO_2 of 35 mmHg at baseline. The pigs were cannulated through the left common carotid artery and the auricular vein. Vital signs (heart rate, arterial pressure, respiratory rate and temperature were recorded every 5 min. Upon placement the arterial line, 15 ml blood sample for each time point were withdrawn for a serum test set, which included a complete blood count (CBC), biochemical variables, blood gas analysis and metabolic profile (**table 1**).

Table 1
Hemodynamic, respiratory and hematologic parameters that were monitored during the study.

Hemodynamic parameters	Systolic Blood Pressure)SBP(
	Diastolic Blood Pressure)DBP(
	Mean Arterial Pressure (MAP)
	Heart Rate (HR)
Respiratory parameters	Arterial Oxygen Saturation (SaO_2)
	End-tidal CO_2 ($ETCO_2$)
	Peak Pressure (Peak P)
	Tidal Volume (Vt)
	Respiratory Rate (RR)
	Mixed Venous Oxygen Saturation (SvO_2)
Complete Blood Count	WBC, RBC, HGB, HCT, MCV, MCH, MCHC, RDW, PLATELETS, MPV, LY%, LY#, MO%, MO#, NE%, NE#, EO%, EO#, BA%, BA#
Biochemistry	ALK.P, AST, ALP, ALB, Total protein, P, CA, CRE, UREA, GLU, CL, K, NA, CPK, TG, CHOL, LDH, DIA, T.BIL, GGTP, Lactate
Coagulation	FIBRINOGEN, PT%, INR, PTT
Endocrinology	TSH, Cortisol

Experimental procedure

A scheme of the study design is presented in Fig. 1. After the animals were stabilized pneumoperitoneum was induced using Veress needle to a pressure of 12 mmHg, and three trocars were introduced to preform laparoscopy. During this procedure a small biopsy was taken from the left lobe of the liver. Then a left lobectomy was preformed throughout a plain in a constant distance of 4 cm from the portal vein. Ten

minutes later a catheter was introduced via the laparoscopic trocar and the treatment was induced to the abdominal cavity in the following order:

Control animals were administered 200 ml saline on the liver remnant and 100 ml were administered on the peritoneum, the small and large bowel. VLVG-treated animals were administered 300 ml of 2% of VLVG which was administered in a similar manner as control animals. All animals were continuously monitored for 8 hours, during which hemodynamic parameters were recorded and blood samples were withdrawn. Liver biopsies were taken at 0, 4 and 8 h time points and were analyzed by a veterinary pathologist. Histopathological changes were scored using semi-quantitative grading (0–4) according to change severity from normal morphology. After 8 hours the animals were sacrificed using an injection potassium-chloride solution.

Alginate

In order to obtain e a free-flowing form of low molecular weight sodium alginate (Very Low Viscosity (high) G alginate), VLVG, we prepared 2% solution by dissolving at room temperature for over-night 6gr of VLVG (NovaMatrix, FMC biopolymers, Drammen, Norway) in 300 ml of saline. Alginate solution was freshly made and appeared clear by eye.

Statistical analysis

Statistical analysis was made by using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics of the variable parameters included mean, median, range and standard deviation. In order to compare the study group to the control in a specific time a-parametric Mann-Whitney test was used. This test uses multiple comparisons, Thus Bonferroni correction should be used, therefore a p value = 0.005 in each point of time would be considered significant. Yet we used an asymptotic p value = 0.05 as a cutoff for significance since it is a feasibility study. To assess if there was a tendency during time we used Friedman's test for a-parametric variables. In order to compare the effect of the treatment (i.e. normal saline VS VLVG alginate) repeated measures ANOVA model was used, and the p value was calculated based on the Greenhouse-Geiser test.

All tests were 2 tailed tests and p = 0.05 was the cutoff for significance. However, due to the relatively small sample p value between 0.05–0.1 was determined as borderline significance.

Results

Hemodynamic measurements

Figure 2 demonstrates significant differences in the hemodynamic parameters between alginate and saline-treated animals. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were significantly ($p < 0.05$) higher in the VLVG-treated group compared to control group (Fig. 2A, C, D). Heart rate (HR) was significantly ($p < 0.05$) decreased in the VLVG group compared to controls (Fig. 2B). These changes were throughout the 8 hours of observation.

Biochemistry

Figures 3–6 shows the changes in level of some laboratory variables. Serum levels of potassium, creatinine, glucose and liver enzymes (ALT, AST) were changed over the time of the study compared to the baseline parameters before the haptic damage ($p < 0.05$). Blood levels of fibrinogen, lactate and cortisol were not significant also demonstrated tendency ($p < 0.05$) (Fig. 6). No significant change in the level of creatinine phosphor-kinase (CPK) was noted and the change in lactate dehydrogenase (LDH) levels over time was nearly significant ($p = 0.08$). The levels of glucose, creatinine, CPK, LDH, cortisol and lactate were lower in the alginate group compared to the control (Figs. 3–6). In addition, mean level of liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were higher in the control group compared to the alginate and the difference increased in the end of the observation (Fig. 4). The difference in mean levels of several biochemical parameters was statistically significant (Figs. 3–6).

Blood count

The levels of hemoglobin did not change significantly over time, neither the levels of white blood cells (WBC), red blood cells (RBC) nor platelets. Mean platelets levels were higher in the VLVG group compared to the controls in all time points. No clear tendency was noted while comparing RBC and WBC levels. The difference of various blood count parameters between groups was not statistically significant at any point.

Pathology

Liver biopsies were taken at the beginning, one hour after the liver damage, 4 and after 8 hours, just before the observation was completed. The analysis of the biopsies demonstrated a pattern of acute neutrophil infiltration in liver septa, variable degrees of hepatic capsular edema, inflammation and subcapsular necrosis (Fig. 7); also few areas of central lobular hemorrhage and necrosis were noted in samples from the alginate group as well as the control (Fig. 8). The samples from the alginate group showed lesser degree of histopathological damage compared to the control as the observation continued, as reflected by semi-quantative grading (Fig. 9).

Discussion

Penetrating abdominal trauma is caused most commonly by gunshot wounds or stab wounds. As the liver takes up a large proportion of the abdominal cavity, up to 30% of penetrating abdominal trauma causes a liver damage (16). Other organs that commonly involved are small and large bowel and vascular structures (16–18).

Mortality from penetrating abdominal trauma is caused by hemorrhage in the short term and sepsis and multi organ failure at the long term (19–22). In the current study we show in a swine model that injection of VLVG into the abdominal cavity after abdominal injury maintained the animals stable and improved important variables in the serum signifying lower degree of organ damage.

Such a model would allow a means to develop and test novel hemostatic agents for the treatment of intra-abdominal bleeding on the battlefield.

In order to establish a valid trauma model, one must demonstrate change in several parameters that reflect the degree of organ damage and shock. Those parameters include hemodynamics, blood biochemical profile, endocrine profile and in our model also markers of hepatic tissue damage (23–26). Also histopathologic samples from liver tissues in a setting of shock demonstrate certain changes such as central lobular necrosis (27). Our model demonstrated changes in all those parameters, thus making it an appropriate model for trauma, hemorrhagic shock and liver damage. Although hemorrhagic shock was induced, the degree of damage was not sufficient to inflict mortality and therefore we could not conclude from this study whether VLVG improved survival. Hemodynamic monitoring revealed lower HR and higher blood pressure values (SBP, DBP, and MAP) in the VLVG–treated animals. Since hemodynamic parameters represent the degree of hemorrhagic shock, our results suggest that animals treated with alginate had lower levels of shock.

In our study we compared treatment with intraperitoneal saline and intraperitoneal VLVG alginate after inflicting trauma to the liver. On our previous studies we showed in 2 murine models the beneficial effect of VLVG (14, 15). These studies demonstrated that the effect of this specific low molecular alginate is not merely physical. These studies also demonstrated that VLVG specifically had effects than other forms of alginates due to different biochemical properties leading better absorption through membranes. Thus, we assumed that VLVG will have a protective effect of all abdominal organs, especially the liver. For example, cortisol levels may rise causing rise in blood glucose levels due to glycogenolysis gluconeogenesis and insulin resistance (28). In our study reduced levels of glucose and cortisol suggest lower degree of physiologic stress in VLVG-treated animals. Although this effect may be due to lower bleeding, it can also imply of anti-inflammatory effect of VLVG. Another biochemical marker for shock is lactate. Lactate is formed in anaerobic metabolism when tissues lack of oxygen due to circulatory failure as in shock, i.e. lactate is a marker for tissue hypoperfusion (29). In our study the mean blood levels of lactate were reduced in the VLVG-treated group, suggesting better tissue perfusion. Fibrinogen, a marker for hemostasis, is a substrate for clot formation, and is known to be low following trauma with massive hemorrhage due to its consumption. Furthermore, lower levels of fibrinogen after hemorrhage are associated with worse outcomes (30, 31). In our study alginate treated animals showed constantly higher levels of fibrinogen suggesting less activation of the coagulation cascades, adding to its ratification that alginate has hemostatic properties.

Trauma is a multi-organ disease that might cause damage distinct organs such as the kidneys. Acute renal failure is common in major trauma and caused by renal hypoperfusion, or late consequences such as rhabdomyolysis or abdominal compartment syndrome. Acute renal failure is represented by serum creatinine concentration (32, 33). In our study at all-time points creatinine levels were lower in the alginate treated group compared to the control group. This may also point that VLVG-treated animals had lower degree of hemorrhage and hypovolemia due to improved hemostasis.

The levels of liver enzymes are well known to correlate with the degree of liver damage in various diseases including trauma (34, 35). In our study the levels of ALT, AST and LDH were higher in the control group when monitoring ended, suggesting prevention of liver injury by VLVG. Importantly, ALT levels were higher in the control group even before infliction trauma. This was caused due to idiopathic preliminary elevation of ALT in two out of four animals in the control group. When histopathologic analysis was done, samples from VLVG- treated groups showed lesser amount of damage at the middle and final hours of the study; although at the beginning the damage within this group was higher. This further suggests the hepatic preserving properties of VLVG.

Our study has several limitations. It was conducted on a total of only 7 animals. This small number did not allow sufficient power for statistical significance. Therefore we used higher cutoffs for p value and comparison of tendency in order to demonstrate the effect of alginate. In addition, due to ethic limitations the length of observation in our study was rather short thus not allowing assessment of survival and long term effects of VLVG.

In conclusion, this small, proof-of-concept study showed that treatment with alginate, specifically VLVG, ameliorated the effects of penetrating abdominal trauma in pigs. Treatment with VLVG improved hemodynamic measures and showed improved metabolic status in lower degree of intra-abdominal organs damage. Further, larger studies are warranted to corroborate these findings.

List of abbreviations: VLVG -Very Low Viscosity (high) G alginate, SBP-Systolic blood pressure, DBP-diastolic blood pressure, MAP- mean arterial pressure, WBC-white blood cells, RBC- red blood cells, LDH-lactate dehydrogenase, ALT- alanine aminotransferase, AST- aspartate aminotransferase.

Declarations

Ethics approval:

This research was approved by the Hebrew University of Jerusalem ethics Committee number: MD16148533, and was adherence to ARRIVE guidelines.

Consent of publication:

not applicable

Availability of date and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Competing interests:

none

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Authors' contributions:

DB, ABY, LW, DN, AE, YM and ES participated in the study concept and design. YM was in charge of the surgical procedures. DN, LW and EA participated in the administrative and technical support. DB was in charge of literature review, statistical analysis and writing. ABY DN and ES participated in critical revision of the manuscript.

Acknowledgment:

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Figures

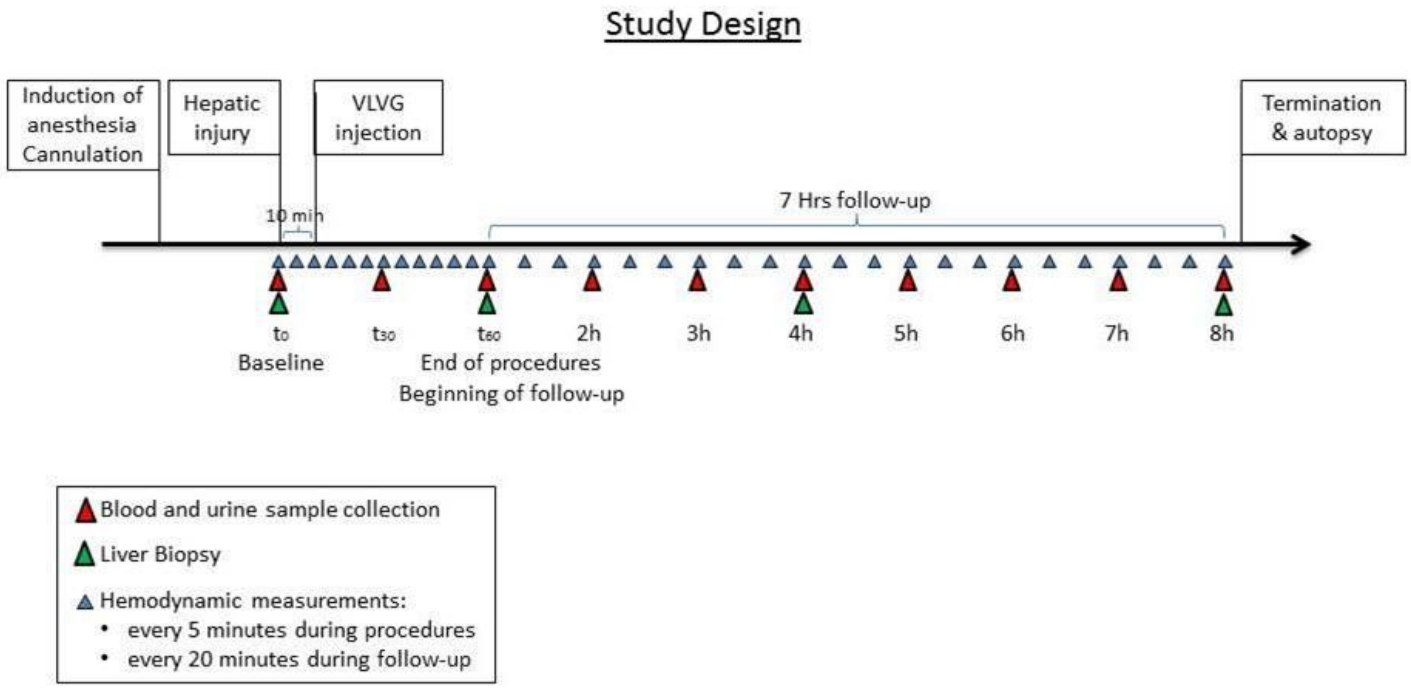
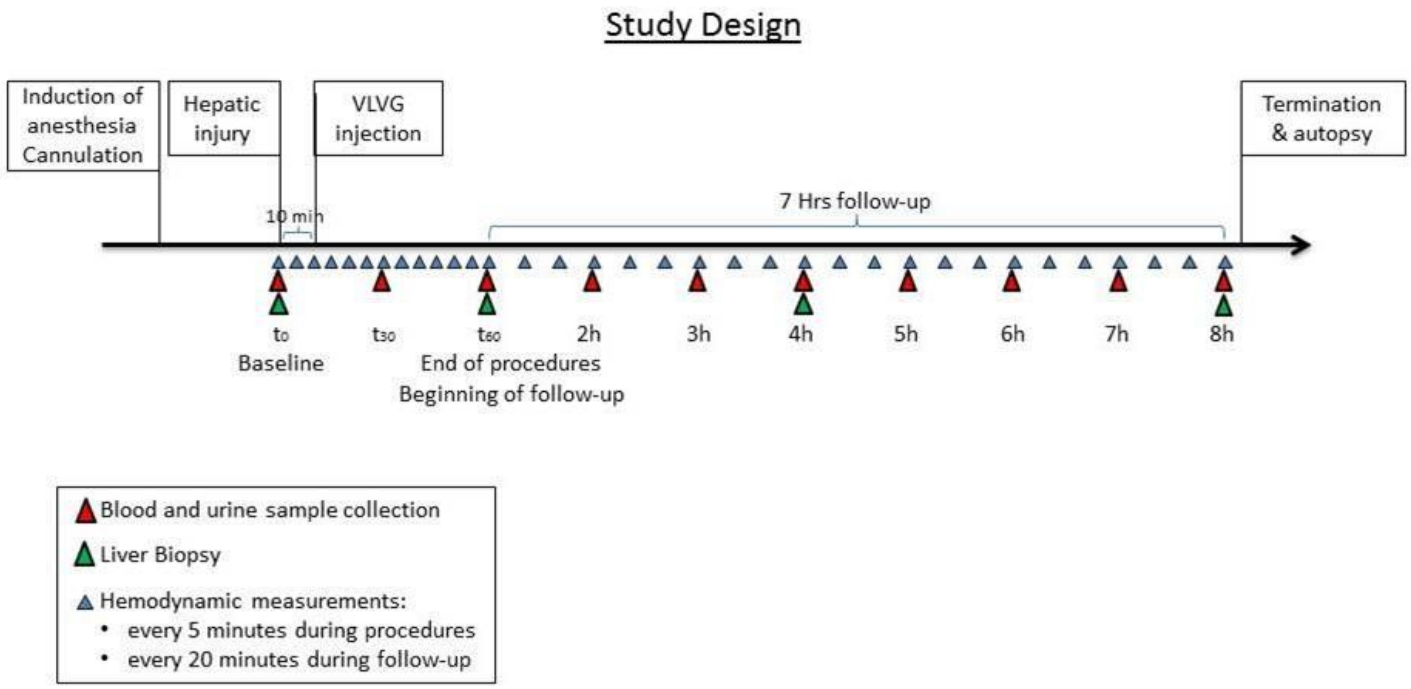


Figure 1

Study design and time line for interventions and monitoring.



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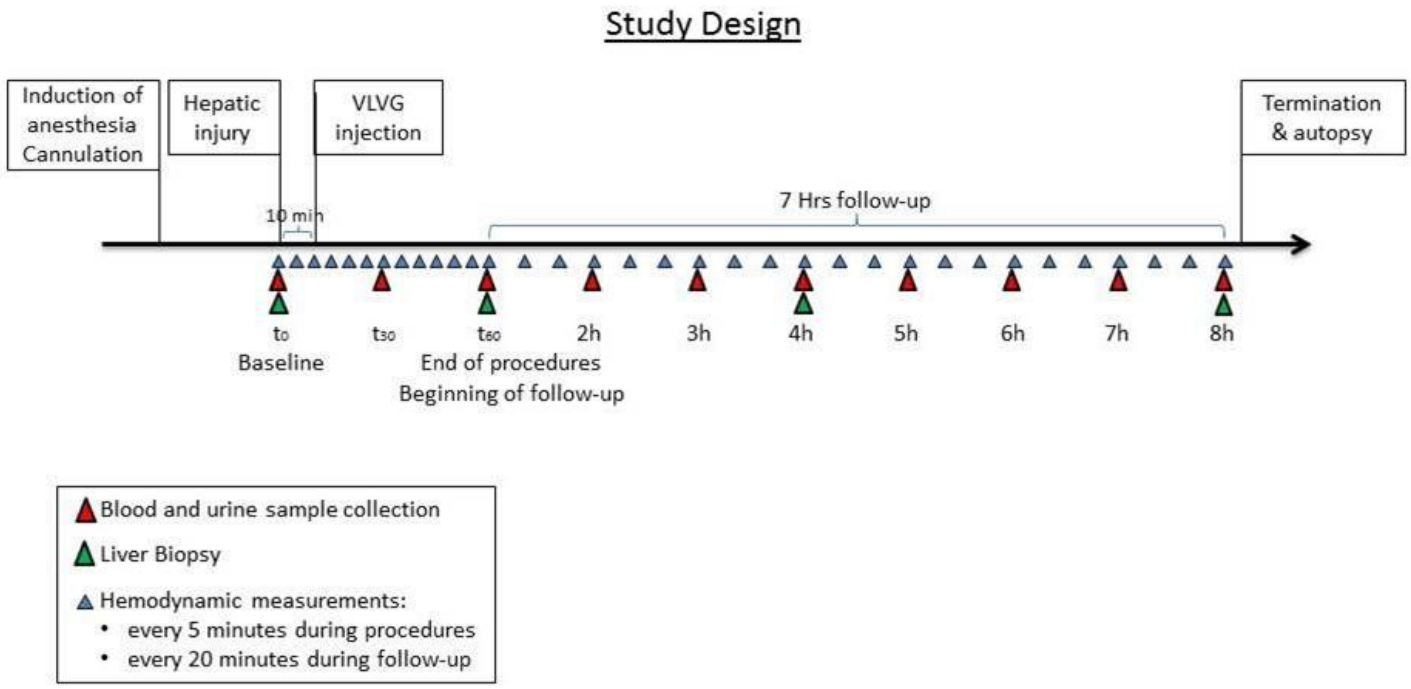

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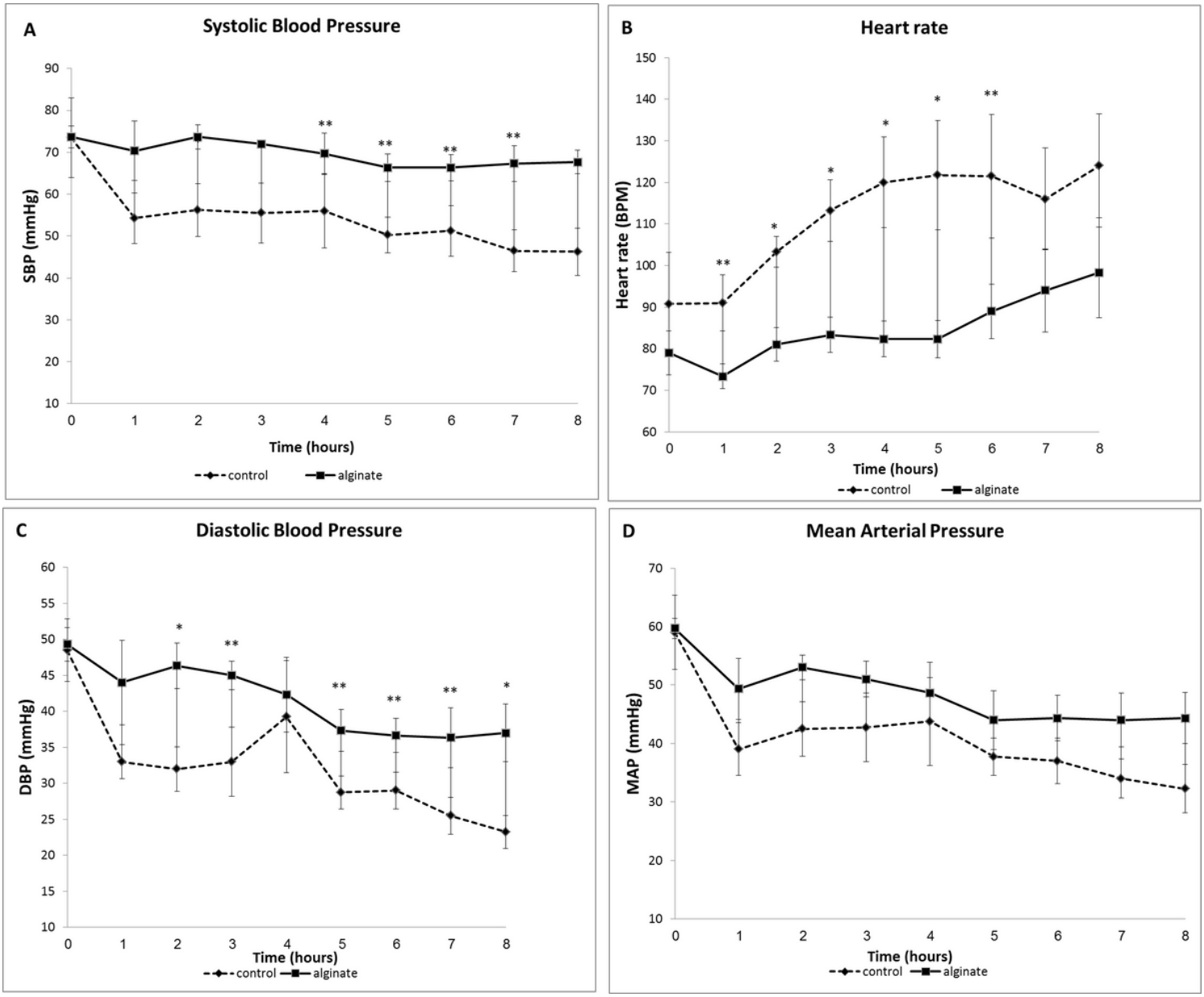
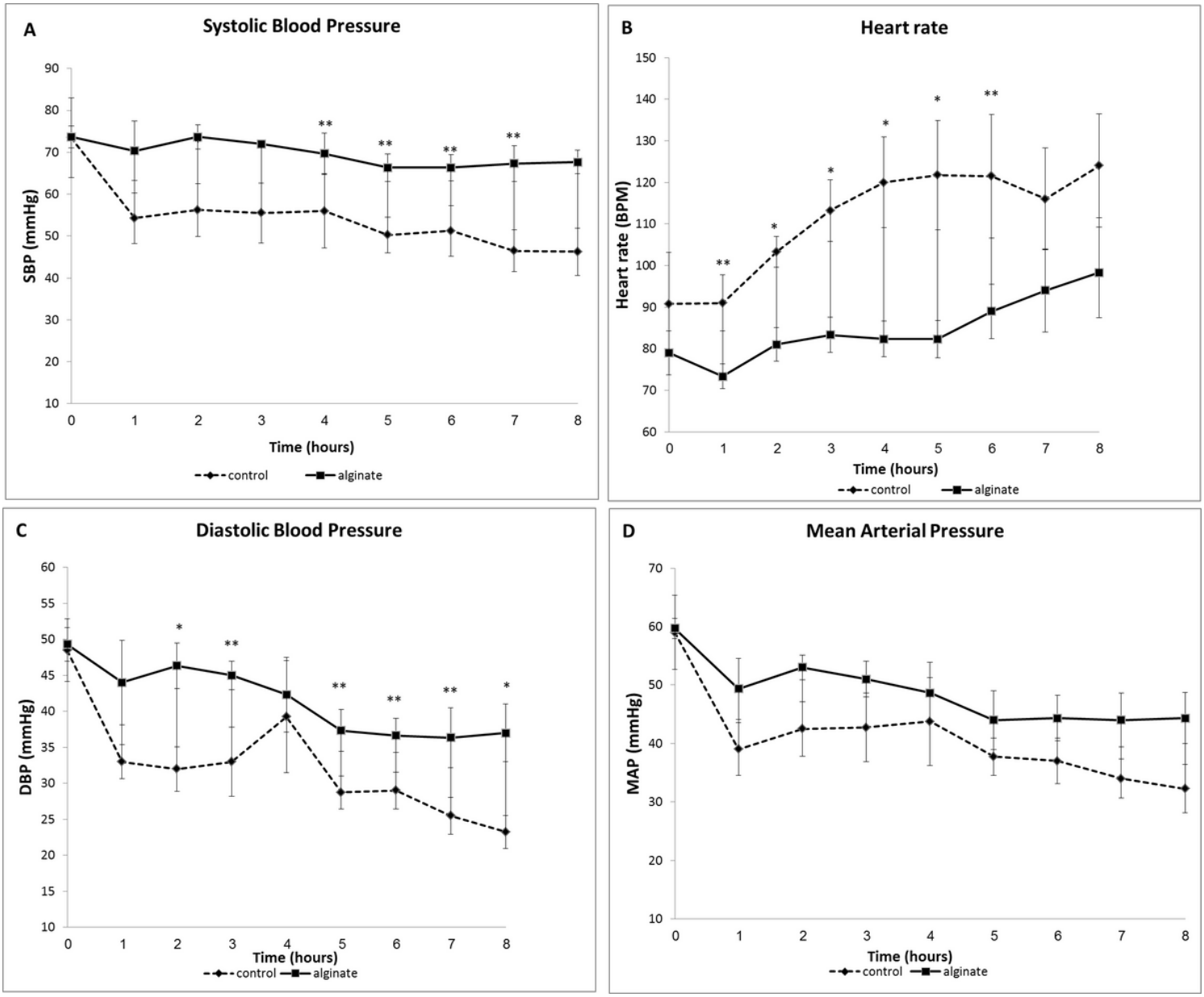


Figure 2

The effect of VLVG alginate on hemodynamic parameters. Points are means +/- standard deviation, n=3 animals in the alginate group, n=4 in the control group. *p<0.05, **p=0.05-0.1.



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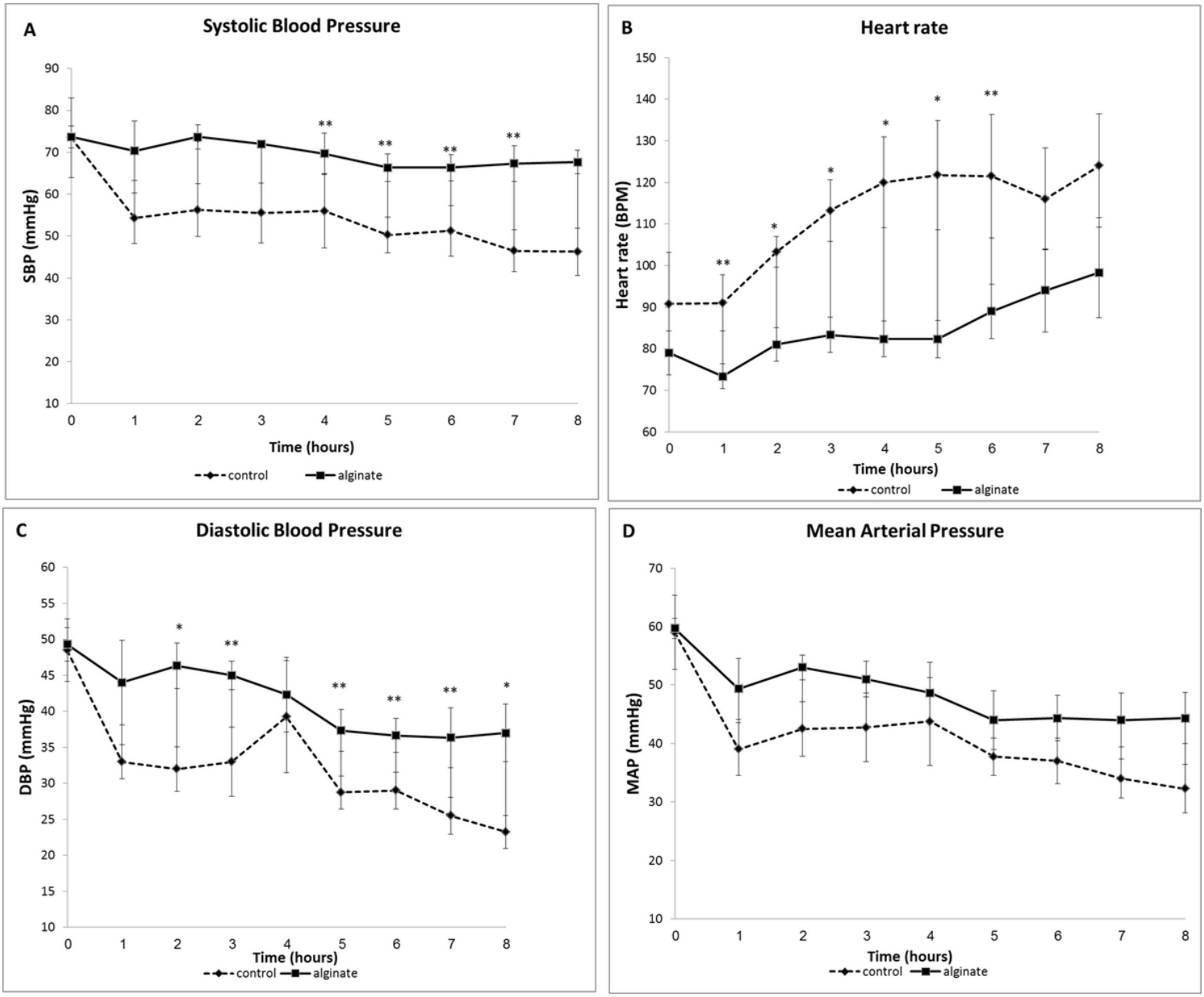

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The effect of VLVG alginate on hemodynamic parameters. Points are means +/- standard deviation, n=3 animals in the alginate group, n=4 in the control group. *p<0.05, **p=0.05-0.1.

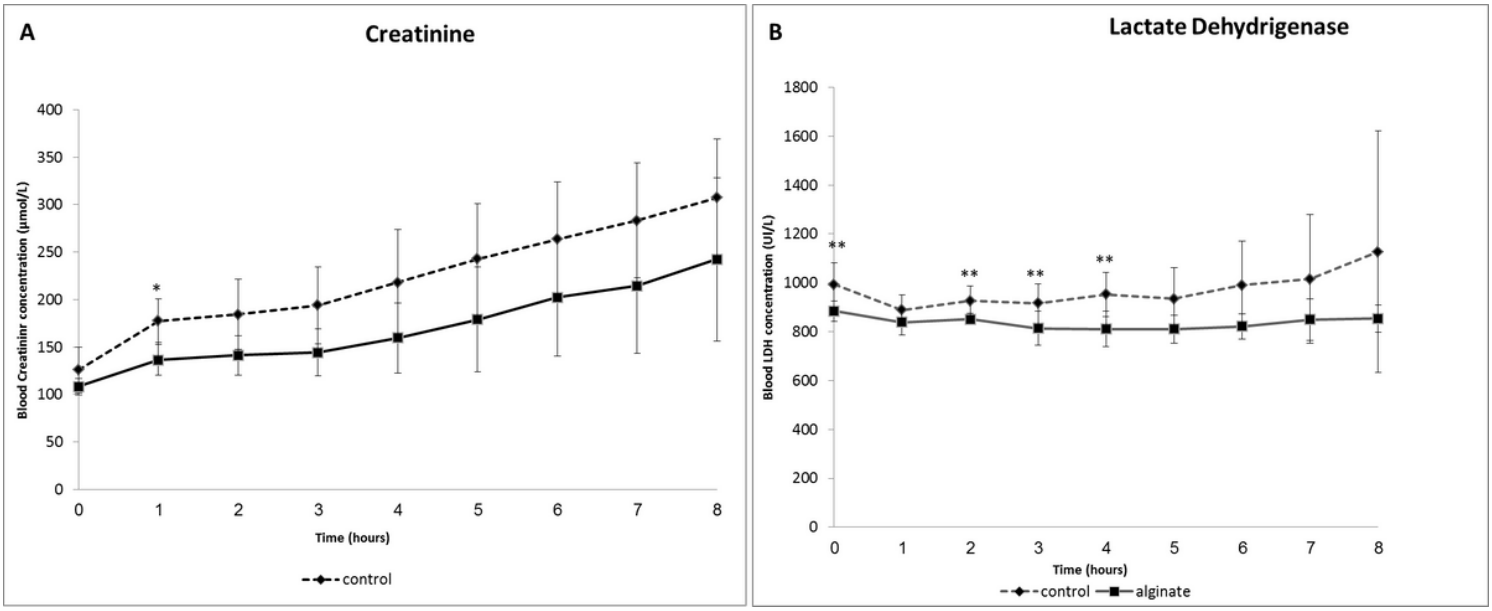
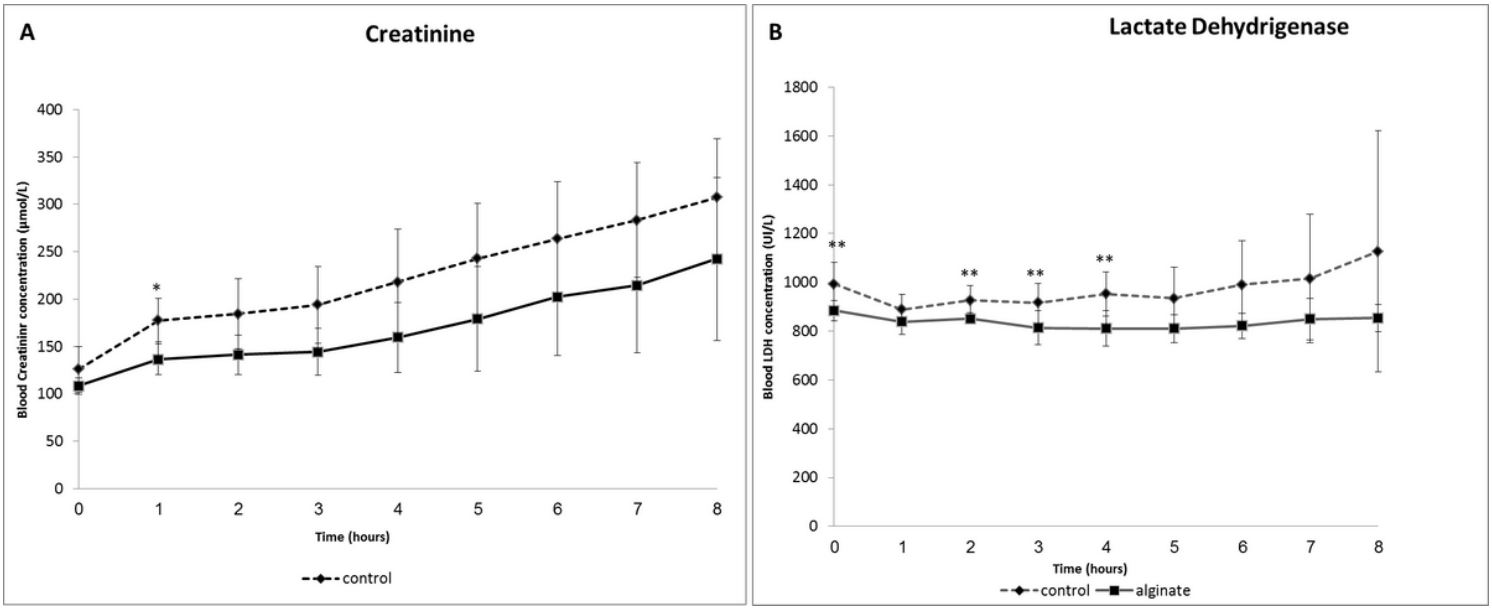


Figure 3

The effect of VLVG alginate on Lactate dehydrogenase (LDH) and kidney function. Points are means +/- standard deviation, n=3 animals in the alginate group, n=4 in the control group. *p<0.05, **p=0.05-0.1.



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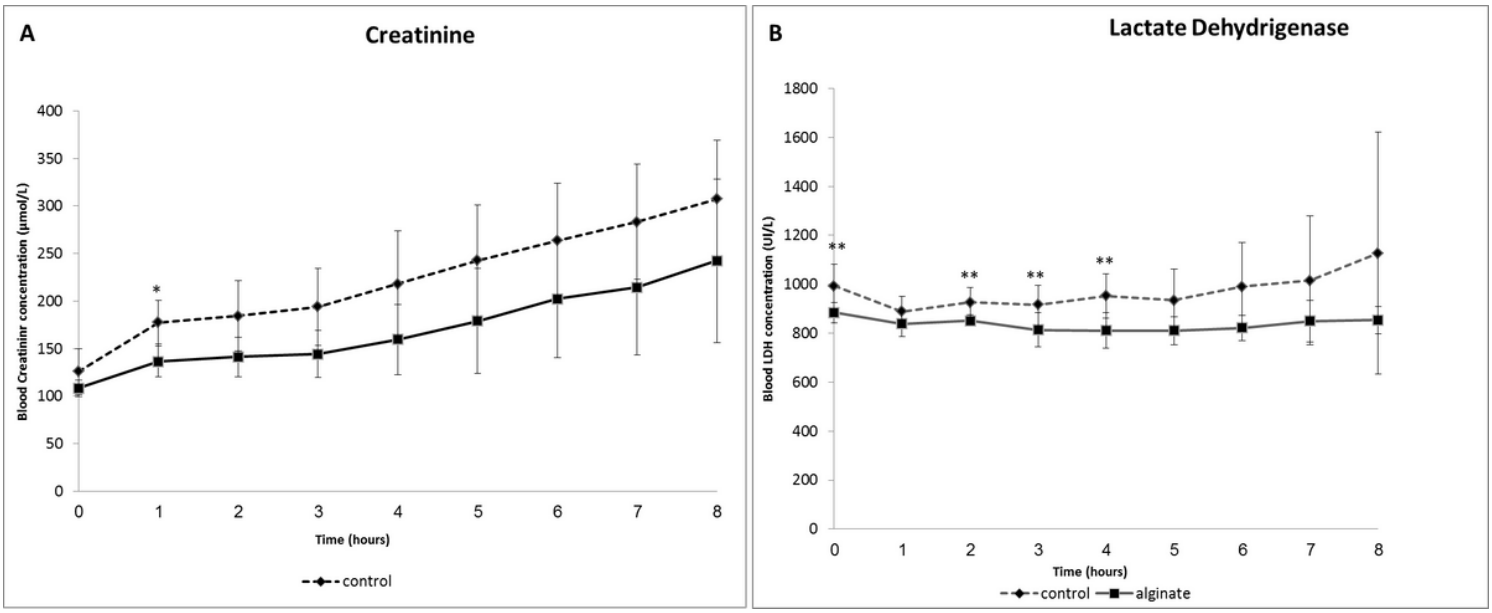

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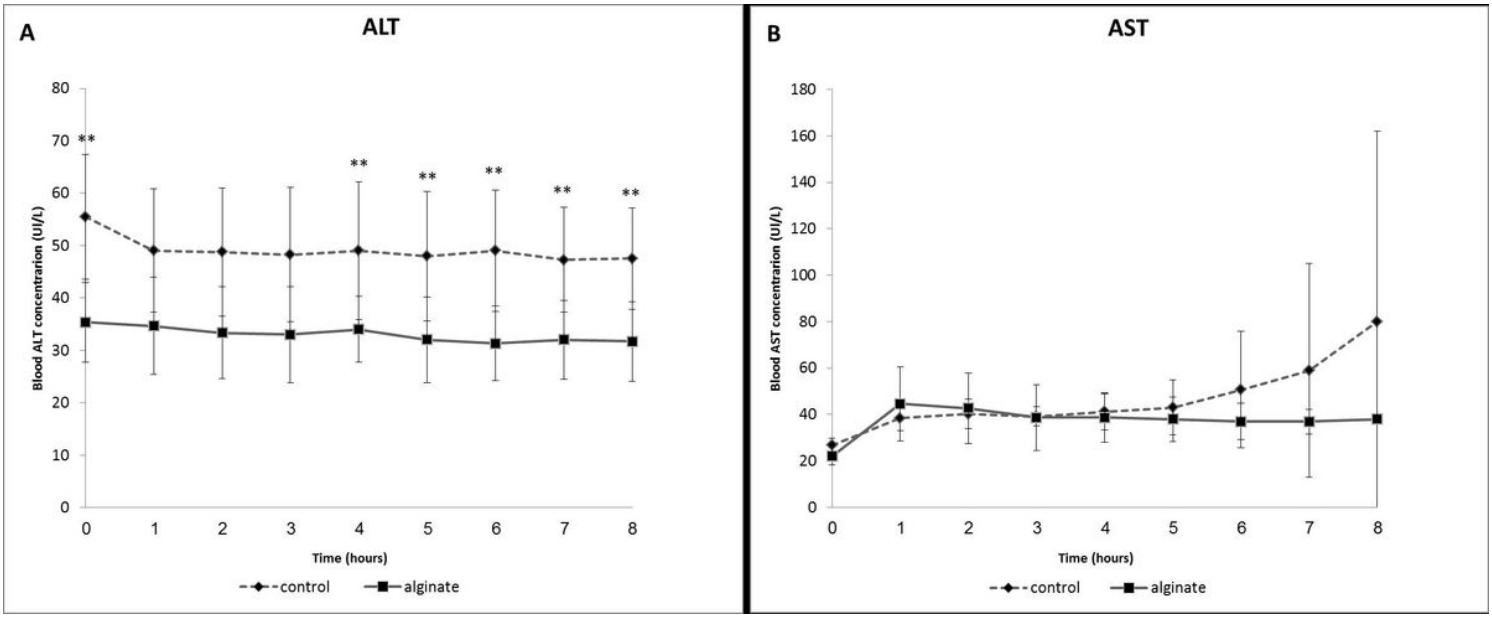


Figure 4

The effect of VLVG alginate on liver enzymes. Points are means +/- standard deviation, n=3 animals in the alginate group, n=4 in the control group. *p<0.05, **p=0.05-0.1.

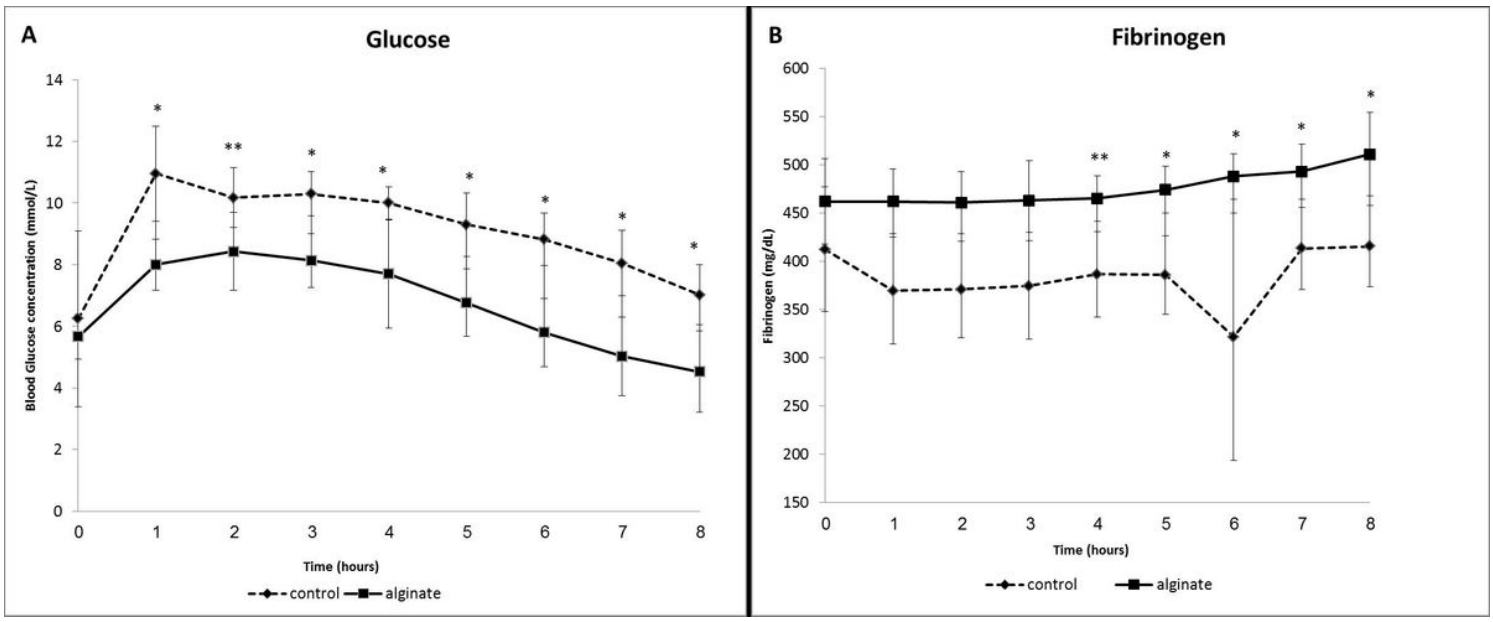
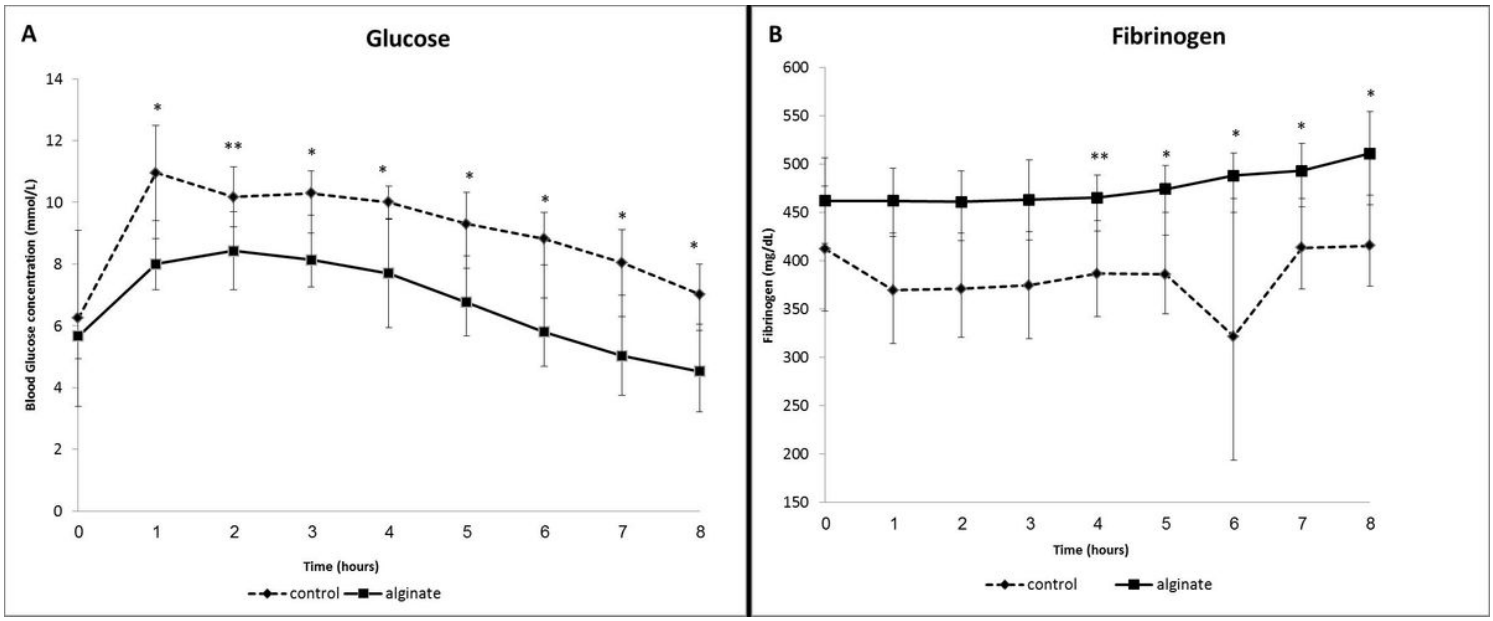


Figure 5

The effect of VLVG alginate on glucose and fibrinogen. Points are means +/- standard deviation, n=3 animals in the alginate group, n=4 in the control group. *p<0.05, **p=0.05-0.1.



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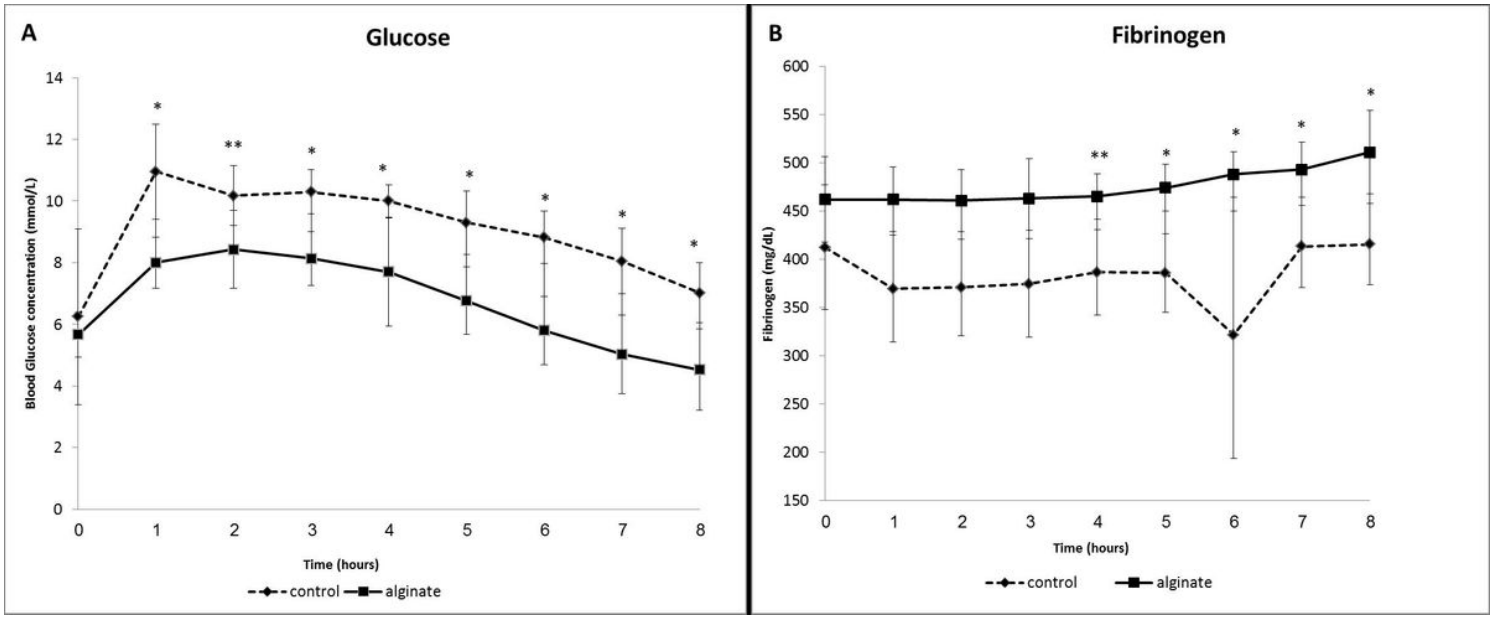

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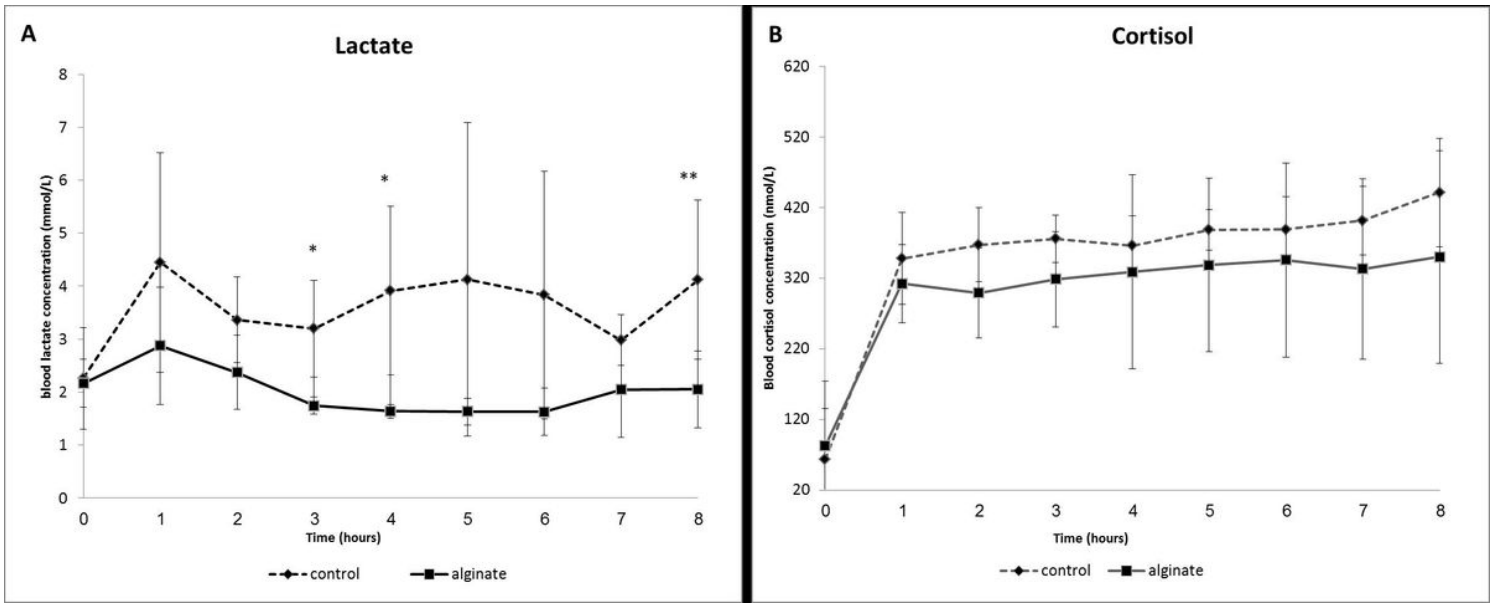

Figure 6

The effect of VLVG alginate on biologic stress markers- lactate and cortisol. Points are means +/- standard deviation, n=3 animals in the alginate group, n=4 in the control group. *p<0.05, **p=0.05-0.1.

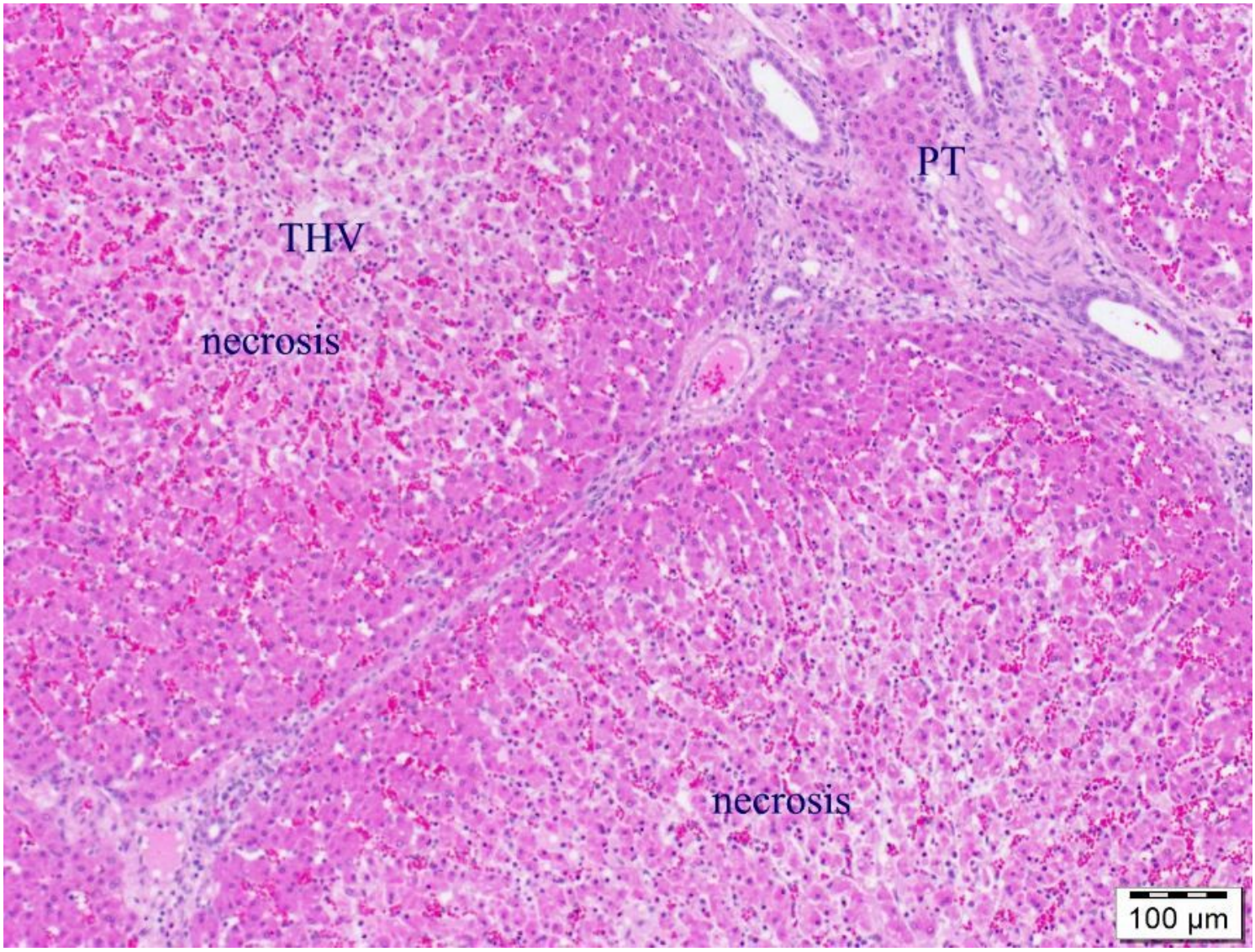

Figure 7

Histologic sample of liver biopsy from an alginate treated animal after 8 from the insult. The sample demonstrates capsular edema and sub-capsular necrosis.

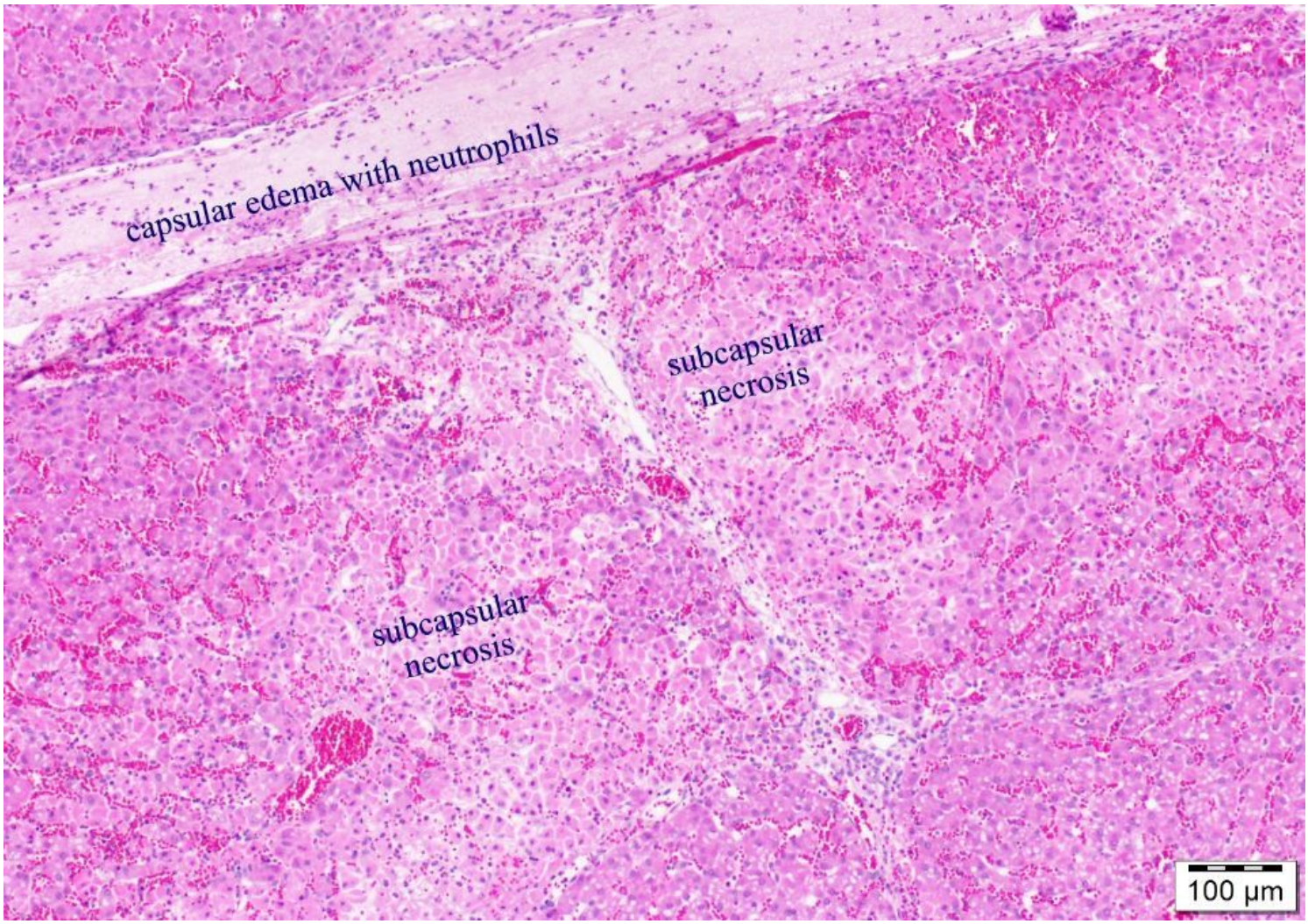

Figure 8

Histologic sample of liver biopsy from an saline treated animal after 8 from the insult to the liver. The sample demonstrates hepatic lobular necrosis. PT- portal triad, THV- terminal hepatic venule.

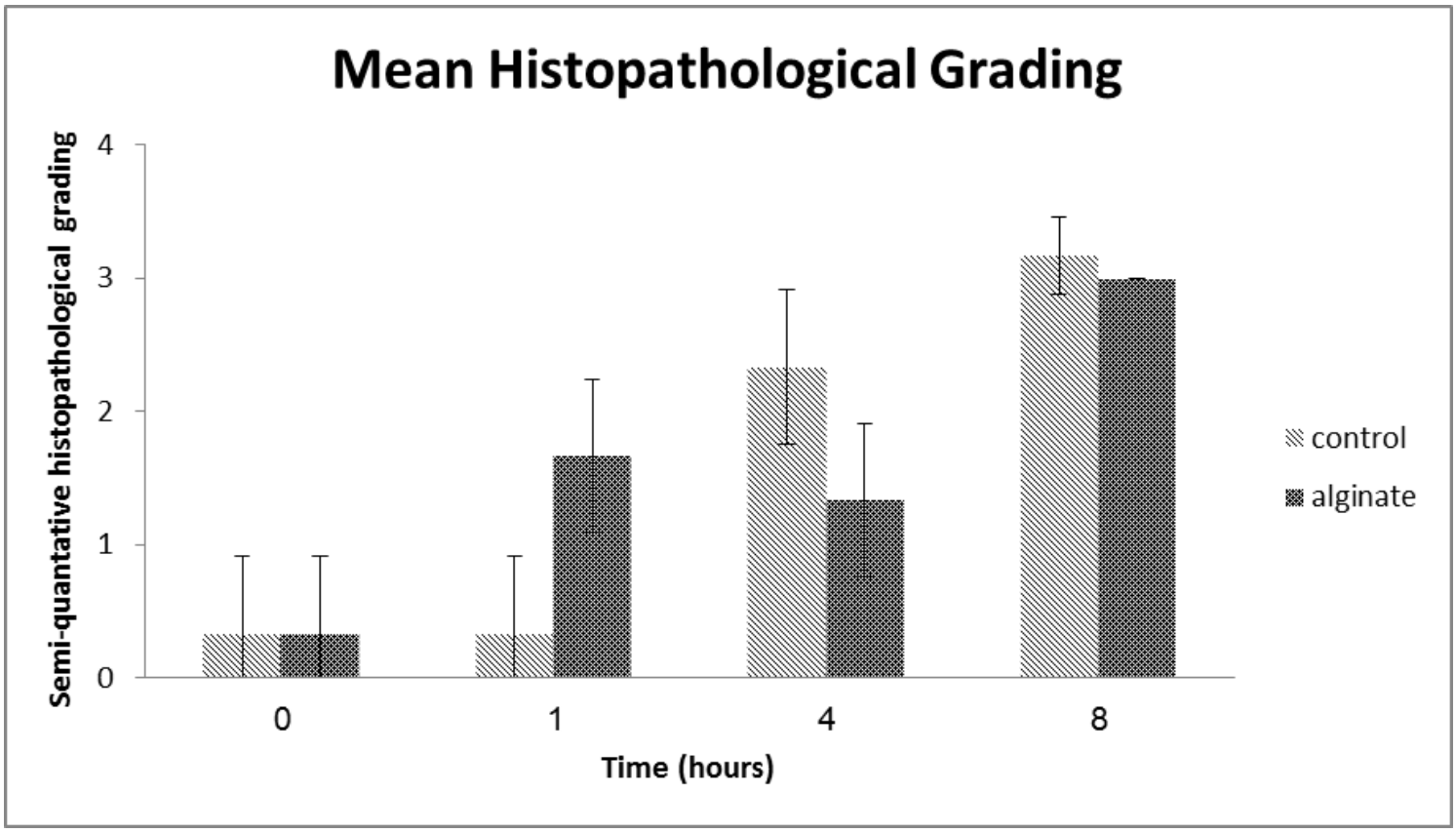

Figure 9

Mean histopathological grading of liver biopsies. Biopsies were taken at the beginning (t=0), after one hour, 4 hours and 8 hours at the ending of the study. Histopathological changes are scored using semi-quantitative grading (0-4), according to change severity: 0: No lesion- normal tissue; 1: minimal change; 2: mild change; 3: moderate change; 4: marked change. Bars are means +/- standard deviation. N=3 animals per group.