



# Impact of some intravenously administered drugs (paracetamol, hydrocortisone, dexamethasone and amikacin) on coagulation hemostasis (in vitro evaluation study)

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## ABSTRACT

**Background:** Normally, the coagulation homeostasis prevents bleeding and retain the blood in the vascular system during periods of injury. Unfortunately, pathological factors, drugs or toxins could affect one or more stages of homeostasis mechanisms leading to bleeding or abnormal thrombi. Evaluation of prothrombin time is a favorable test for the screening of extrinsic coagulation mechanism whilst activated partial thromboplastin time measurement is a global coagulation screening method for intrinsic factor.

**Material and Methods:** Blood samples were withdrawn from healthy adults volunteers for clotting times measurements from collected plasma. The effect of paracetamol, hydrocortisone, dexamethasone, and amikacin at different concentrations on coagulation homeostasis was in vitro investigated and compared to control and positive control.

**Results:** High concentrations of all tested drugs except amikacin prolong significantly activated partial thromboplastin time, whilst the effect on the prothrombin time was conflicting.

**Conclusions:** Paracetamol, hydrocortisone, dexamethasone, and amikacin could prolong clotting time expressed in prolongation of activated partial thromboplastin time comparable to the anticoagulants drugs.

**Keywords:** coagulation, drugs, prothrombin time, clotting factors, in vitro

## INTRODUCTION

The coagulation homeostasis could be thought of as complex cascading reactions involving the development of enzymes from precursors with the aid of cofactors, ions, and phospholipid surfaces were the final product was fibrin meshwork clot (1). Normally, such mechanisms prevent bleeding and retain the blood in the vascular system during periods of injury. Unfortunately, different pathophysiological processes may disrupt coagulation homeostasis lead to the development of abnormal thrombi in the blood vessels leading to circulatory disorders like deep-vein thrombosis, myocardial infarction, stroke, and pulmonary embolism (2). There are several causative factors, drugs or toxins could affect one or more stages of homeostasis mechanisms leading to bleeding or abnormal thrombi (3). Thus, coagulation homeostasis is ordinarily conserved in check by different physiological antithrombotic processes blanket substantially the entire coagulation cascade. Antithrombin, protein C, and protein S wield their anticoagulants action by affecting and inhibiting clotting factors (4).

Evaluation of prothrombin time (PT) is a favorable test for the screening of extrinsic coagulation mechanism whilst APTT measurement is a global coagulation screening method for intrinsic factor assessment that considered as a common pathway of the coagulation system. PT has been used to monitor and follow up on patient's response to anticoagulant therapy. However, due to PT is fluctuating depending on thromboplastin utilized in lab assays, International Normalized Ratio (INR) is presently the accepted gold standard for evaluation of warfarin therapy (5,6).

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Recently, drugs-induced coagulation disorders have been gained more attention in different articles to explain the direct or indirect thrombogenic effect of a variety of drugs consumed for the treatment of clinical disorders (7,8).

Venous thrombosis is a common side effect of large number widely prescribed drugs, corticosteroids and contraceptive pills can lead to blood disorder in long term therapy (9,10). Actually, multiple drugs may lead to unexpected increased risk of blood disorders, Girolami et al. clearly indicate and summarise the potential clinical significance of such problem, the authors focus on drugs with possible effect on coagulation cascade: gonadotropins, Cortisone, estradiol, nonsteroidal anti-inflammatory drugs, Clozapine antipsychotic, anabolic hormones, desmopressin, chemotherapeutic agents, in addition to other herbal and energy drinks. All these compound may lead to venous thrombosis as potential adverse effects (8).

On the contrary, sometimes drugs lead to unexpected bleeding tendency due to the reticence of platelet aggregation, coagulation hemostasis, and prolongation of PT (11). In a case report Dootson GM. et al found that oral isotretinoin may accelerate fibrinolysis and disturbed coagulation factors (12). Thus it is essential and mandatory to continuous monitoring of coagulation cascade very closely in patients with chronic use of drugs in the treatment of chronic illness (13). Actually, the present study was designed for in vitro evaluating the direct effect of some widely prescribed intravenous drugs on coagulation hemostasis explained by PT, APTT and INR.

## **MATERIALS AND METHODS**

### **Chemicals and Reagents**

Thrmppo Genex (USA), PT and APTT kits (BIOLABS France), Heparin (5000 unit/ml) Leo pharma Denmark), Paracetamol vial 10 mg/ml (PANPHARMA France), amikacin (500mg/2ml (Deva turkey), dexamethasone 8mg/2ml (Deva turkey), and Hydrocortisone vial 100mg/2ml (Haemofarm company).

### **Preparation of Plasma**

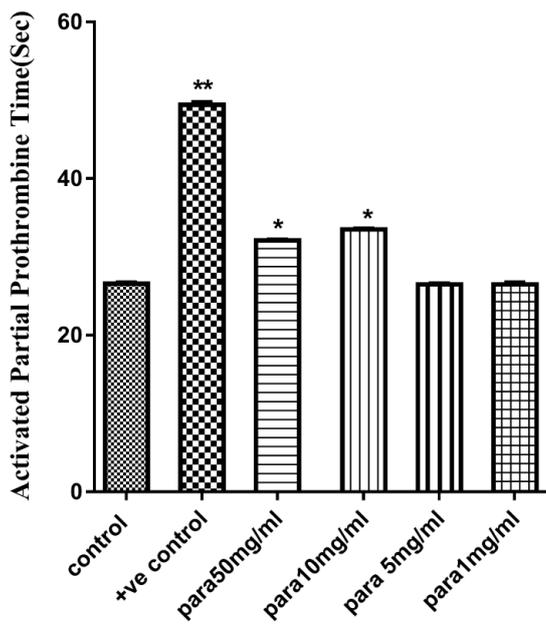
After obtaining written informed consent and ethical approval from the college of pharmacy, Basrah University, blood samples were withdrawn from healthy adults volunteers without a history of chronic diseases and free from chronic medications intake. All participants fasted overnight and they are medication-free for at least one week prior to blood collection. Blood collected into sodium citrate tube immediately centrifuged at 25000r/min for 10 min according to manufacturer's instructions for PT and APTT measurements from collected plasma. The effect of paracetamol, hydrocortisone, dexamethasone, and amikacin at different concentrations on coagulation homeostasis was investigated in vitro consequently on day of blood collection without plasma freezing.

### **Study Design (PT/INR and APTT Measurements)**

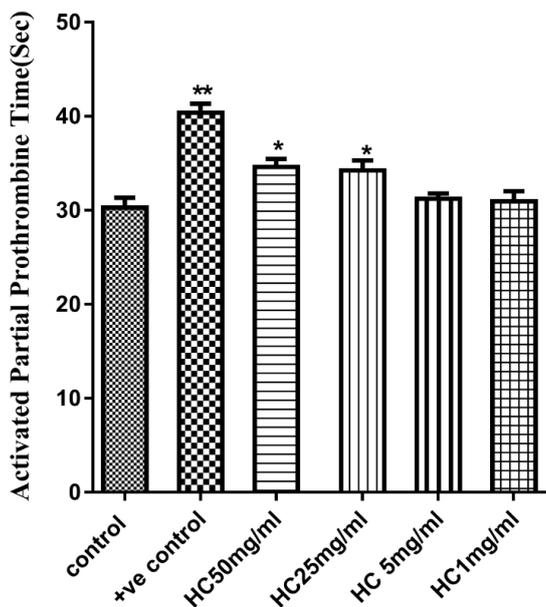
According to Félix-silva et al with slight modification (14), 0.1 ml of 4 tested drugs with a series concentrations test samples as following: paracetamol (50, 10, 5, 1) mg/ml, hydrocortisone (50, 25, 5, 1)mg/ml, dexamethasone ( 2, 1, 0.5) mg/ml, amikacin (250, 125, 62.5, 31.25) mg/ml, in addition to 0.1 ml of heparin(1IU/ $\mu$ l) as positive control, 0.1 ml normal saline as negative control group and plasma alone (for INR measurement) were added to 0.9 ml plasma then incubated for 10 min at 37c for subsequent PT and APTT analysis according to kit manufacturer instructions. Measurement of PT/INR and APTT reflect the direct effect of investigated drugs on extrinsic and intrinsic pathways respectively (15). For PT measurement, 200  $\mu$ l was pre-warmed for 15 min at 37 °C and added to each tested samples and clotting time using coagulometer was recorded in seconds. APPT reagent was pre-warmed for 2 min at 37 °C and added to the samples and clotting time recorded using coagulometer after adding Ca-solution kit. The INR values were calculated by dividing the sample PTover the mean normal PT (geometric mean of the plasma only PT values) raised to the power of international sensitivity index ( a function of the used thromboplastin reagent which is in our study equal to 1.65). This step was carried out in order to standardize the PT values and eliminate the differences resulted from using variable thromboplastin of different sources.

### **Statistical Analysis**

The values were assessed statistically using ordinary one-way ANOVA analysis with Sidak's multiple comparisons test. Values are expressed as Mean  $\pm$  SD, Values with  $P < 0.05$  were considered significantly different. The statistical analysis was done by using software GraphPad Prism for Windows (version 7.0).



**Figure 1:** The effect of paracetamol in different concentrations on the activated partial thromboplastin time. \*\*  $p < 0.0001$ , \*  $P < 0.05$ . Para: Paracetamol, +ve control: heparin ( $1IU/\mu l$ )



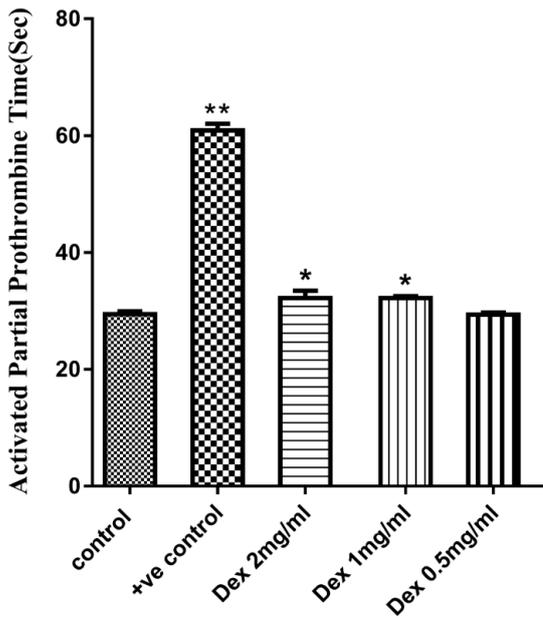
**Figure 2:** The effect of hydrocortisone in different concentrations on the activated partial thromboplastin time. \*\*  $p < 0.0001$ , \*  $P < 0.05$ . HC: hydrocortisone, +ve control: heparin ( $1IU/\mu l$ )

## RESULTS

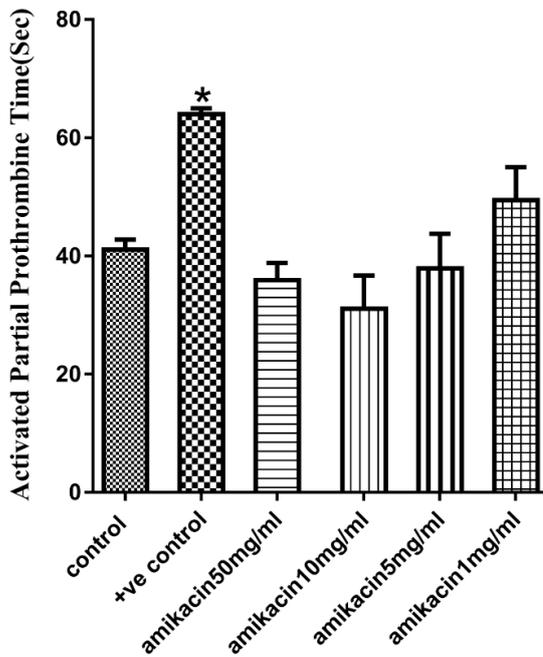
In the present study, PT/INR and APTT were utilized to assess the direct coagulation effect of common widely prescribed drugs for the treatment of different illness. Such drugs when administered by intravenous route may lead to direct interference with coagulation homeostasis could adversely affect physiological coagulation cascade.

As shown in **Figure 1** paracetamol in 50 and 10 mg/ml prolong clotting time significantly in APTT test ( $32.1 \pm 0.1$  and  $33.5 \pm 0.1$ ) sec respectively versus it is level in control ( $26.6 \pm 0.1$ ) sec demonstrating possible anticoagulant activity, such increment in APTT significantly less than that observed in +ve control group with addition of heparin ( $49.4 \pm 0.32$ ) sec. Whilst low concentrations of paracetamol show no significant effects compared to control.

Hydrocortisone in 50 and 25 mg/ml prolong significantly APTT clotting time ( $34.6 \pm 0.85$  and  $34.23 \pm 1.05$ ) sec respectively compared to control ( $30.27 \pm 1.05$ ) sec but such values are lower than that observed in +ve control group  $40.37 \pm 0.95$ . Lower concentrations of hydrocortisone 5 and 1mg/ml showed no significant difference against control as summarized in **Figure 2**.



**Figure 3:** The effect of dexamethasone in different concentrations on the activated partial thromboplastin time. \*\*  $p < 0.0001$ , \*  $P < 0.05$ . Dex: dexamethasone, +ve control: heparin (1IU/ $\mu$ l)

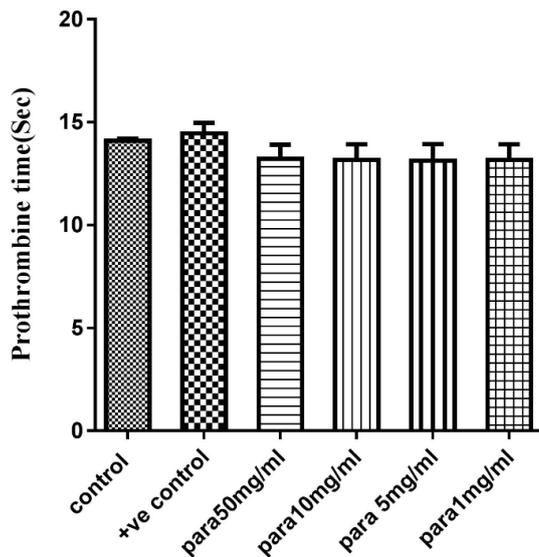


**Figure 4:** The effect of amikacin in different concentrations on the activated partial thromboplastin time, +ve control: heparin (1IU/ $\mu$ l)

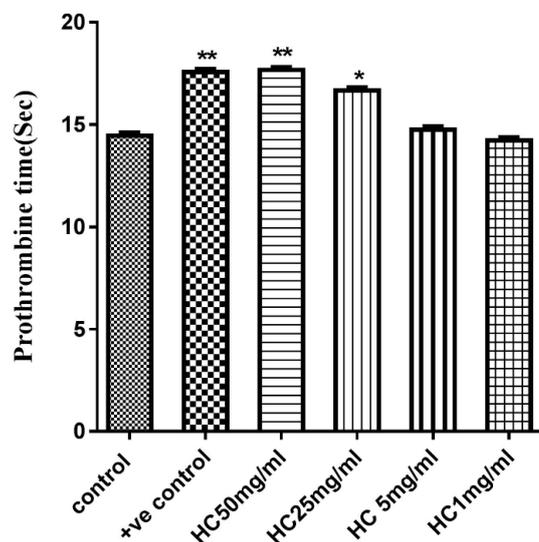
Regarding the effect of dexamethasone on APTT, 2 and 1 mg/ml prolong significantly clotting time ( $32.17 \pm 1.29$  and  $32.17 \pm 0.35$  sec) respectively compared to control ( $29.47 \pm 0.45$  sec) whilst the highest APPT value observed in the +ve control group ( $60.9 \pm 1.11$  sec). 0.5mg/ml of dexamethasone showed no significant discrepancy was observed compared to the control group as appearing in **Figure 3**.

**Figure 4** clearly summarized the direct effect of amikacin on APTT clotting time, no significant effect had been observed in all tested doses compared to control whilst the APPT level reach  $63.97 \pm 1$  sec in the +ve control group and considered significantly high in comparison with remaining groups.

In order to get complete idea about the impact of drugs on the coagulation system, the PT test was performed and INR value was calculated. In regard to paracetamol and dexamethasone, no significant effect had been detected in all tested concentrations compared to control and +ve control groups as shown in **Figures 5, 7** and in **Table 1**. On the other hand, the PT level in hydrocortisone 50mg/ml concentration prolongs PT ( $17.67 \pm 0.15$  sec) as comparable to +ve control ( $17.57 \pm 0.15$  sec). 25mg/ml of hydrocortisone prolong PT ( $16.67 \pm 0.15$  sec) versus control but it is less significant

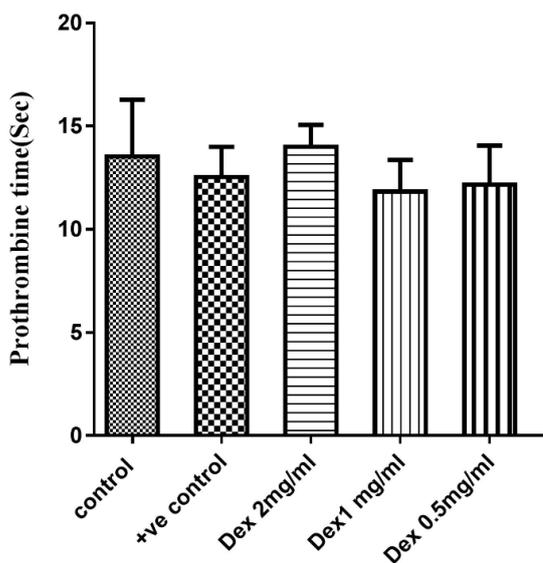


**Figure 5:** The effect of paracetamol in different concentrations on the prothrombin time. Para: Paracetamol, +ve control: heparin (1IU/ $\mu$ l)

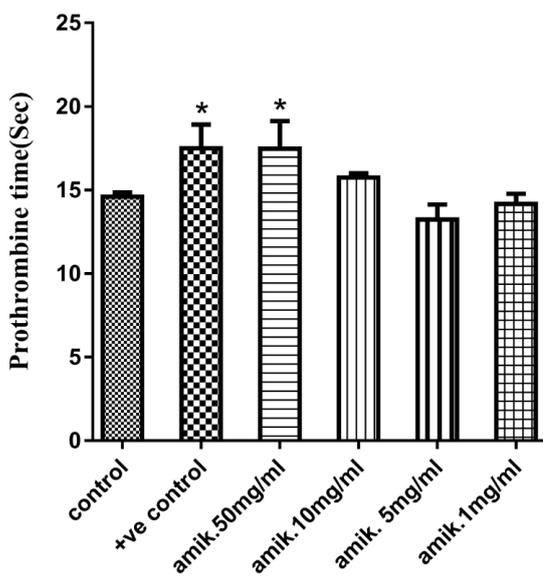


**Figure 6:** The effect of hydrocortisone in different concentrations on the prothrombin time. \*\*  $p < 0.0001$ , \*  $P < 0.05$ . HC: hydrocortisone, +ve control: heparin (1IU/ $\mu$ l)

than that observed in +ve control as shown in **Figure 6**. Regarding the effect of hydrocortisone on INR, there was a significant increase in ratio in all evaluated concentrations except in 1mg/ml compared to control, Such ratios were less significant compared to +ve control as shown in **Table 1**. The high concentration of amikacin 50mg/ml prolongs PT significantly  $17.47 \pm 1.6$  sec compared to control. Such effect seems to be as comparable to +ve control group  $17.5 \pm 1.4$  whilst the remaining amikacin concentrations displayed no significant differences compared to control as indicated in **Figure 8**. Regarding INR, amikacin in all tested concentrations showed no significant effect compared to plasma as displayed in **Table 1**.



**Figure 7:** The effect of dexamethasone in different concentrations on prothrombin time. Dex: dexamethasone, +ve control: heparin (1IU/ $\mu$ l)



**Figure 8:** The effect of amikacin in different concentrations on prothrombin time, \*  $P < 0.05$  +ve control: heparin(1IU/ $\mu$ l)

**Table 1:** Effect of different concentrations of tested drugs on INR, values were expressed as Mean  $\pm$  SD, heparin as +ve control and plasma as control. <sup>a</sup>: represent significant difference compared to control. <sup>b</sup>: represent significant difference compared to +ve control. Para=Paracetamol, HC:Hydrocortisone, Dex: Dexamethasone, amik:amikacin

Control (mean $\pm$ SD)	+ve Control (mean $\pm$ SD)	Tested drugs(mean $\pm$ SD)			
Plasma	Heparin 1 IU/ $\mu$ l	para50mg/ml	para10mg/ml	para5mg/ml	para1mg/ml
0.902 $\pm$ 0.013	1.067 $\pm$ 0.06	0.9217 $\pm$ 0.078	0.9117 $\pm$ 0.091	0.911 $\pm$ 0.092	0.9147 $\pm$ 0.087
plasma	Heparin 1 IU/ $\mu$ l	HC50mg/ml	HC25mg/ml	HC 5mg/ml	HC1mg/ml
0.948 $\pm$ 0.017	1.2 $\pm$ 0.02	1.48 $\pm$ 0.02 <sup>ab</sup>	1.343 $\pm$ 0.02 <sup>ab</sup>	1.1 $\pm$ 0.02 <sup>ab</sup>	0.902 $\pm$ 0.017 <sup>b</sup>
plasma	Heparin 1 IU/ $\mu$ l	Dex 2mg/ml	Dex1 mg/ml	Dex 0.5mg/ml	
0.9457 $\pm$ 0.029	0.8557 $\pm$ 0.162	1.027 $\pm$ 0.126	0.781 $\pm$ 0.167	0.82 $\pm$ 0.203	
plasma	Heparin 1 IU/ $\mu$ l	amik50mg/ml	amik10mg/ml	amik5mg/ml	amik1mg/ml
1.17 $\pm$ 0.05	1.46 $\pm$ 0.194	1.457 $\pm$ 0.229	1.223 $\pm$ 0.0351	0.922 $\pm$ 0.103 <sup>b</sup>	1.028 $\pm$ 0.068 <sup>b</sup>

**DISCUSSION**

The high incidence of hemorrhagic and thrombotic disorders may be caused by the suboptimal use of drugs. This study was carried out for in vitro evaluation the direct coagulation effect of some drugs (paracetamol, dexamethasone, hydrocortisone, and amikacin) on hemostasis variables represented by PT and APTT. To avoid and raise knowledge about

drug clotting factors interference in intravenously administered drugs may worsen coagulation cascade which may lead to subsequent health issues.

In the present study, paracetamol at high concentrations prolongs clotting time expressed in PT and APTT significantly comparable to that observed by anticoagulants. It prevents the generation of prostaglandin mostly in the central nervous system this action by inhibition of COX-1 (16). However, peripheral side effects that occur with NSAIDs, like peptic ulcers and impaired coagulation hemostasis less appeared with acetaminophen (17). An explanation of our finding that an unstable toxic metabolite of paracetamol called N-acetyl-para-benzoquinone imine (NAPQI) could slow up the function of vitamin K processed cross-linked with glutathione depletion affecting clotting factors 2, 7, 9, and 10, which are important in blood coagulation process (18). The current study well correlates with the results of Dakheel S (19) *in vivo* study, she reveals that long term paracetamol administration prolong PT and INR in those patients consumed paracetamol to relieve their headache. In fact, free radical generation and glutathione depletion are the exact explanation of our *in vitro* findings (20). Toxicologically, the intravenous administration of paracetamol has been linked with clinical mishaps including death. At this point there are restrictions on its intravenous use compared to oral, intramuscular and rectal routes (21).

Regarding the effect of glucocorticoids on coagulation hemostasis is not resolved and still controversial. Some authors reported that corticosteroids (dexamethasone) lead to a procoagulant state in healthy individuals (22). Whilst others reported an increase in coagulation time by enhancing antithrombin 3 activity associated with decreased incidence and complication of abnormal clotting through nuclear receptors related mechanism (23). Actually, the results of the current study revealed that high doses of both H.C and dexamethasone increased significantly clotting time in APTT test compared to control. Such prolongation was not observed in the PT test except in high doses of H.C. this seems to be comparable to that observed in A. Colao et al. and S. Koutroumpi et al. where PT value usually maintained in Cushing patients or prolonged in certain circumstances (24,25). Mechanistically, our findings need to be explained nonetheless only a few articles are available in this area. However, more than one study made a conclusion that corticosteroids decrease clotting time and increased the chance of thrombosis (26-28).

Corticosteroids (CS), such as prednisone, hydrocortisone and dexamethasone decreased the inflammation, and thus the thrombosis was reduced, although they were thrombi inducer in non-inflammatory diseases, like Cushing's syndrome this may be due to increases in factor 8, fibrinogen, and von Willebrand factor, with decreased fibrinolysis which may not be offset by increase in anticoagulant proteins, C and S (28). Indeed, our results regarding the effect of corticosteroids on coagulation hemostasis were not in agreement with an investigation in which the long-term administration of glucocorticoids lead to hypercoagulability in rats (29). All the available information about the effect of corticosteroids on clotting time are the results of *in vivo* animal and human studies. In the present study direct *in vitro* evaluation of corticosteroids effect on coagulation had been done. This is an important cause of controversy, but the logical explanation of our results is the relation and effect of CS on antithrombin 3. This exactly means that CS affects the expression of the regulatory element of antithrombin 3. This came in tune with D. Barrett et al., they suggest that management with CS might be a good pharmacological alternative to exogenous administered antithrombin 3 formulation (23).

Regarding amikacin, we did not observe any significant effect on APTT clotting time whilst the only high concentration of amikacin prolong PT as compared to the +ve control group,

Generally, Amikacin could block the effects of ADP induced platelet aggregation by inhibiting the release and activation of fibrinogen or probably the inhibition of endogenous clotting factor as well (30). In contrast to our finding, another animal study in goats reported that intravenous amikacin in a dose of 10 mg/kg body weight was associated with increasing in the fibrinogen level and decreasing clotting time in the PT test (31). In conclusion, paracetamol, hydrocortisone, dexamethasone and amikacin in high concentration prolong clotting time significantly expressed in APTT without any effect observed in PT except for high doses of hydrocortisone and amikacin. *In vivo* studies are needed to support our *in vitro* finding that intravenously administered tested drugs could affect coagulation hemostasis.

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