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Venous Catheterization Experimental Model in Rabbits: Histological Alterations in the Catheter Region

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Abstract

Central venous access is one of the most common surgery procedures worldwide, especially in pediatric surgery. Local and regional complications as the result of venous catheter permanence time are frequently described as: thrombosis, infection, edema and local cellulite, movement and loss of the catheter. Other severe complications such as endocardiac and hemorrhagic lesions are also described and considered the cause of catheter early removal. In the literature few studies have addressed vascular and perivascular lesions and complications as the result of central venous access to peripheral veins, given the difficulty of setting up venous catheterization experimental models to study blood vessels and perivascular tissue alterations after catheterization. In the present venous catheterization experimental model, rabbits were divided into two groups based on the time that the venous catheters were maintained in their veins. Group a composed of 7 New Zealand male rabbits was submitted to a 15-day treatment; and the 6 New Zealand male rabbits of group B were treated during 90 days. Both groups presented similar inflammatory conditions since there was no significant difference between groups. Therefore, the results may well suggest that the endothelial inflammatory reaction could have developed at an early initial short period and by maintaining the catheter, the inflammatory reactions would have decreased or disappeared. Aimed at studying these vascular and perivascular alterations in venous catheterization, the present study proposes an experimental rabbit model that allows the analysis of differences in local vascular and perivascular histological variations and compares histological differences be-

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tween both venous catheterization groups each of them with different periods of treatment.

Keywords

Experimental Surgery, Central Venous Catheter, Venous Thrombosis, Phlebitis

1. Introduction

Despite high complication rates, central venous access is largely used in neonatal and pediatric and neonatal intensive care units and several surgical procedures [1] [2]. After numerous peripheral punctures, vessels that are peripheral and superficial cannot bear neither the catheter presence nor the infusion of innumerous solutions, be them electrolytes, vasoactive drugs, lengthy parenteral nutrition or antibiotics [3] [4].

Several complications have been described, not only at the moment of the catheter insertion procedure, but also for the period of time it is inserted in the vein and at its removal [5]. Lesions such as venous laceration, dissection of the venous wall and accidental arterial puncture, pneumothorax, hematoma, and even death were described as complications during the catheter introduction procedure [6].

Endothelial lesion, venous stasis, and blood hypercoagulability characterize Virchow triad (1856) that results in thrombophlebitis and deep vein thrombosis (DVT). When venous catheters are utilized, endothelial lesions and venous stasis are the factors that start the thrombotic process [7] [8]. The endothelial trauma in turn starts coagulation chain reactions through three paths: exposure of the subendothelial tissue activating tissual thromboplastin, release of interleukin-1 (**IL**-1), and tumor necrosis factor (TNF) by endothelial cells. Inducers of endothelial adhesive molecules, interleukin-1 (**IL**-1), and tumor necrosis factor (TNF) are essential for the adhesion of leucocytes to the endothelium surface before they move to adjacent tissues [8] [9].

A large number of superficial thrombophlebitis cases occur after chemical lesions of the vessel intima are triggered by intravenous injections or infusions of different solutions and different concentrations, as in the case of venous catheters [10]. In thrombophlebitis initial phase, leucocytic infiltrate prevails in the vein and thrombus and is spread to neighboring tissues particularly skin and subcutaneous cellular tissue which explains its clinical symptoms, lower friability and high thrombus consistency [11].

Therefore, the intralumen catheter is a chain reaction agent of constant endothelium irritation, exposing the matrix and increasing the risk of thrombi formation throughout the vascular system which may depend on the catheterization time and localization [12] [13].

The catheter inserted in the vein is recognized as a foreign object, which triggers an immediate inflammatory response with the formation of a fibrin layer and deposition of other plasmatic proteins on the object [14]. This tissual reaction is followed by platelet deposition and aggregation. In spite of being an expected event, this process may evolve into the formation of thrombi inside the catheter [14] [15].

A great variety of materials are employed in the manufacturing of catheters. Some materials such as Teflon® or polyethylene are well known thrombogenic compounds, whereas catheters made of silicone are safer, biologically inert and more resistant to thrombosis [15]-[17]. Each catheter is designated by the vessel and the place in which its distal extremity is located, that is, peripheral or central; by the permanence time (temporary, short term, long term or permanent); by its insertion localization (subclavian vein, femoral vein, internal jugular vein, basilic and femoral peripheral veins); as well as peripheral insertion central catheters—PICC. Moreover, catheters can also be denominated by their route starting on the skin up to the vessel (tunnelized *versus* non-tunnelized), or any other special feature, as the presence or absence of a cuff, impregnation with heparin, antibiotic or antiseptic agent and the number of lumens) [18].

In all these cases, the presence of the catheter in contact with the vascular wall is the main source of persistent irritation that results in endothelial lesion, formation of coagulation sites and thrombosis [19]. It seems that the catheter introduced in the vein is initially recognized as a foreign body that is rapidly covered with fibrin and plasmatic proteins followed by deposition of platelets that forms a thrombus on the catheter surface [19].

The objective of the current study is to present an experimental venous catheterization model in rabbits that allows the analysis of alterations in vascular and perivascular veins with catheters of polyethetraflurethylene

(PTFE) 17 GA by comparing two groups with different catheter permanence time.

2. Material and Method

This study was submitted to the Ethical and Research Committee in Animals of Medical Science and Health Faculty of the Catholic University of São Paulo (FCMS, PUC/SP), Brazil in August, 2012 and was approved in September, 2012.

New Zealand male rabbits weighing approximately 2.5 kg were selected. The animals used in this study come from the vivarium of FCMS, PUC/SP. On the experiment day, the animals were sedated to general anesthesia with Ketamine base-50 mg/ml (Ketalar®-Cristália do Brasil) at a dose of 35 - 40 mg/kg associated to Xylazine 10 mg/ml (Coopazine®-Coopers Brasil Ltda.) at a dose of 5 - 6 mg/kg, both administered by injection with an insulin syringe and 20 G needle on the thigh lateral muscle. The association of these drugs produces a sedative effect that lasts for about 1 hour, enough time to perform the surgery. Additionally, general anesthesia was also given in the incision site an injectable solution of Bupivacaine 0.5% without vasoconstrictor (adrenaline), which provides both intra and postoperative analgesia.

All animals presented phlebotomy in the right external jugular vein (**RjV**) under general anesthesia with the same polytetrafluorethylene catheter 17 GA on the day marked as day zero. After this period, the animals were divided in two groups: the first group, denominated **group A**, was represented by rabbits that were reoperated on the 15th postoperative day to collect material. The second group, denominated **group B**, was represented by rabbits that were reoperated on the 90th postoperative day after the catheter insertion. The **Control** group for histological analysis was represented by the left external jugular vein (**LjV**) of the same rabbit, which was not manipulated.

At the beginning of the procedure, the animal is placed on a saddle with its head flexed to the left exposing the entire right lateral cervical region. Antisepsis of the animal skin was done with alcohol at 70% and it was subsequently isolated with a sterile fenestral field.

In order to increment the procedure precision, the surgeon used a magnifying glass 3.5 Neitz Instr. Co. Ltd. The incision of approximately 2 - 3 cm was made on the right lateral cervical region with a scalpel blade n. 11 perpendicularly to the Right External Jugular Vein (**RjV**) 3 - 4 cm below the animal's submandibular edge by palpating the sternocleidomastoid muscle and starting the incision medially to this muscle. Subsequently, RjV was dissected and fixed in the cranial and caudal directions with a 5 - 0 polypropylene cord without excessive traction. RjV was opened by sectioning its wall at 45˚ towards the cranium, leaving the proximal edge more vertically and facilitating the introduction of the PTFE 17GA catheter (**Figure 1**). The catheter distal end was introduced 5 cm into the vein and a Nylon 5 - 0 cord was used to tie the catheter in its interior. The catheter external extremity was bent and tied with the same cord to avoid blood leakage in the postoperative period (**Figure 2**). Suture of the animal skin was done with Nylon 5 - 0 cord with 4 separated stitches.

At reoperation, harvest day, according to the catheter permanence time of each group, the rabbits were anesthetized and an incision was made in the same position of the previous procedure. A segment of 4 - 5 cm was removed from RjV together with the fibrotic tissue developed around it with the catheter inside the vein (**Figure 3**). The whole surgical specimen is comprised of RjV, the catheter and adjacent tissues (study pad) and preserved in a sterile flask containing form ol at 6%. The same procedure was carried out on the left side to remove LjV, which is the Control group. Then, the incision was sutured with polypropylene 5 - 0 and the animals were taken to the vivarium, given that they were not euthanized.

Thirteen rabbits were operated, 7 from **group A** (15 days with the implanted catheter) and 6 from **group B** (90 days with the implanted catheter). It's necessary to declare that we had restrictions from Ethical and Research Committee in Animals due to this is a study in the graduation level. That's the reason for a small number of animals.

In order to carry out microscopic structure analysis, slides were prepared with the study pads that were collected in reoperation for histological analysis. Two different dyes were used to obtain better structure identification: 1) stained with hematoxylin-eosin (HE); and 2) dyed with **orcein**, which allows arteries to be distinguished from veins, since in some cases fibrosis and vascular alterations are possibly caused by the presence of the catheter, which could modify the tissues. The slides were analyzed under an optical microscope with 40 times magnification.

The results were referred for statistical analysis with Fisher's Exact Test for small samples and unpaired data.

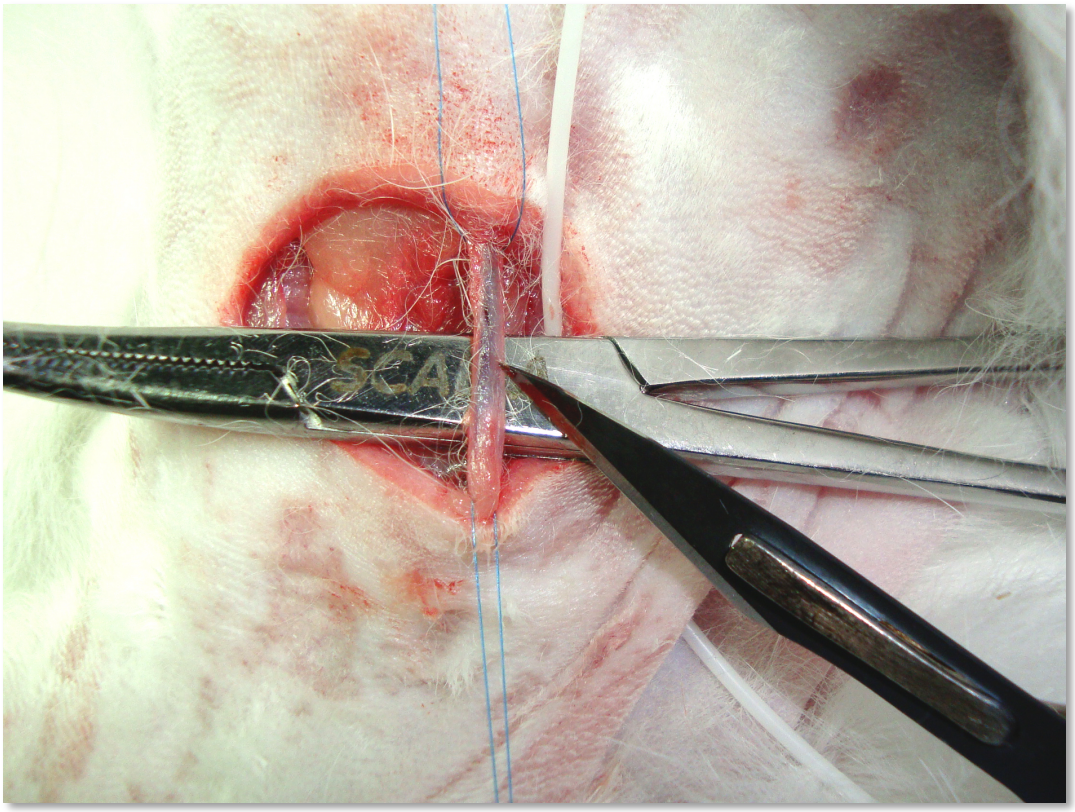

Figure 1. Shows RjV was dissected and fixed in the cranial and caudal directions with a 5 - 0 polypropylene cord without excessive traction. RjV was opened by sectioning its wall at 45° towards the cranium, leaving the proximal edge more vertically and facilitating the introduction of the polyethylene 20 G catheter.

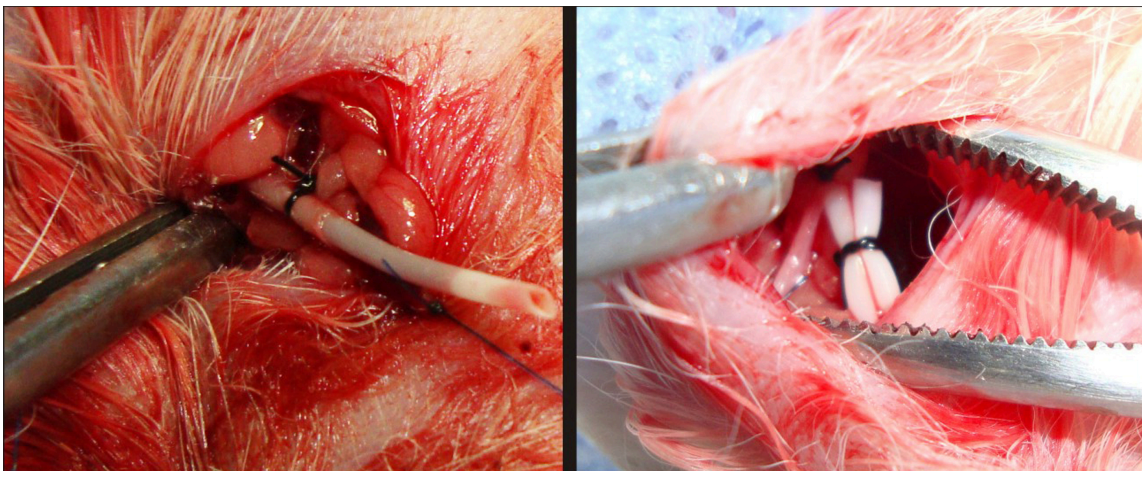

Figure 2. The catheter distal end was introduced 5 cm into the vein and a Nylon 5 - 0 cord was used to tie the catheter in its interior and around the vein. The catheter external extremity was bent and tied with the same cord to avoid blood leakage in the postoperative period. Black arrow shows RjV and white arrow shows bent and tied catheter.

3. Result

During the second surgery for the collection of study pads, no macroscopic differences were observed by comparison in the circumjacent region of the catheterized vessel of the two **groups A** and **B**. Both groups presented fibrosis in the region surrounding the catheter that covered the vein and small adjacent blood vessels. All the

catheters remained in the same place of their insertion in RjV, and none were fractured. Moreover, no veins were transfixed, nor disrupted in the initial procedure or during the catheter permanence time [3]. The contralateral vein that was not manipulated (**Control** group) didn't show any alteration in all samples.

Slides analyses showed a similar pattern of endothelial erosion and inflammatory reaction on the vascular wall of both **groups A** and **B**. Inflammatory reaction in rabbits of **group B** presented less acute cellular than **group A** which can be explained as a resolution of the inflammatory process through the 90 days or evolution to fibrosis given the longer remaining time of the catheter.

The most frequent histological alteration that was found in rabbits of both groups (**A** and **B**) was endothelial erosion and inflammatory infiltrate (**Figure 4**), as described below in **Table 1** and **Table 2**. It was settled that **Mild erosion** is that lesion that presented in less than 50% of the surrounding endothelium dislocation of cells seen on the microscope. On the other hand, Extensive erosion was settled the lesion that presented almost 100% of the surrounding endothelium dislocation.

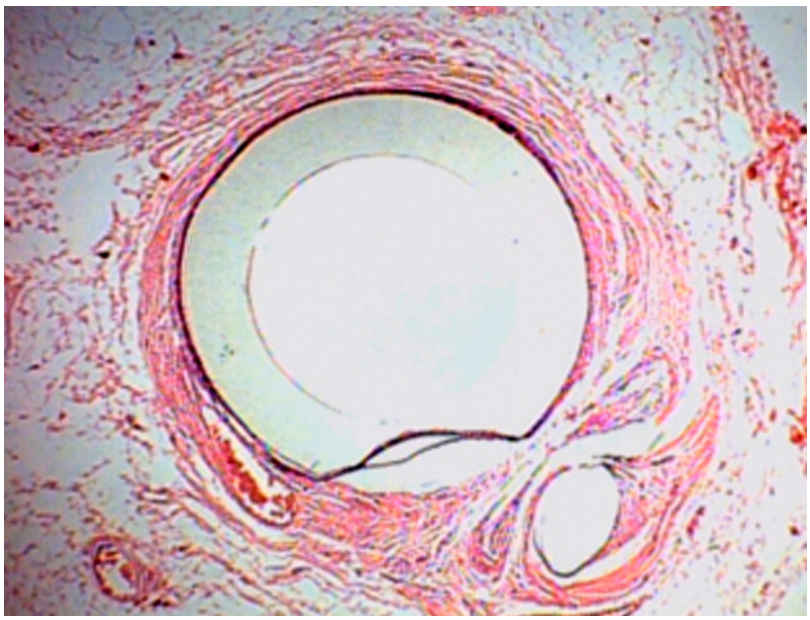

Figure 3. A segment of 4 - 5 cm was removed from RjV together with the fibrotic tissue developed around it with the catheter inside the veinin rabbits of the **group B** (90 *days of catheterization*), hematoxylin-eosin stain. In this image can be seen a transverse slice of the catheter inside the vein (*black arrow*), size 40×.

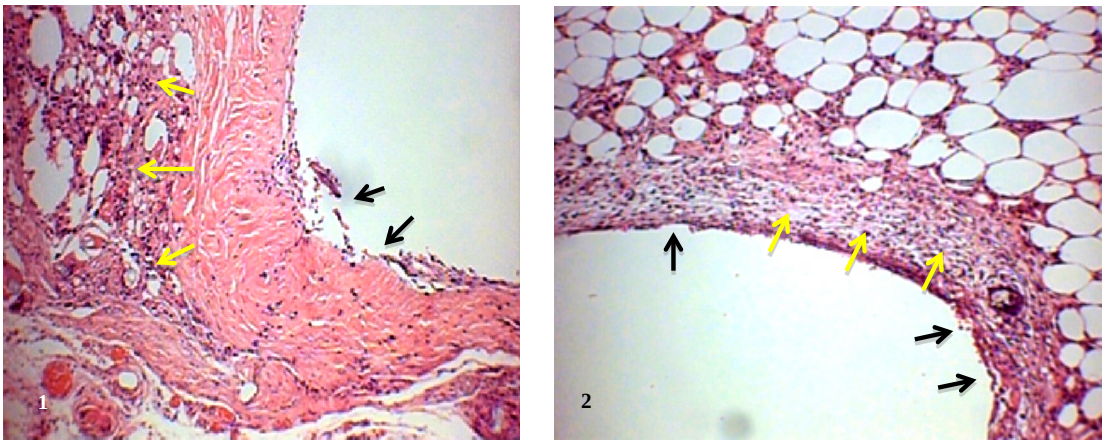

Figure 4. The most frequent histological alterations that were found in rabbits of both groups (**A**, **Figure 1** and **B**, **Figure 2**) were inflammatory infiltrate (yellow arrows) and endothelium erosion (black arrows), hematoxylin-eosin stain, size 40×.

Table 1. Shows the most frequent histological alteration that was found in rabbits of the **group A**.

Group A	Histological alterations (15 days of catheterization)
1	Extensive erosion on the endothelium and discreet inflammatory infiltrate
2	Extensive erosion in the endothelium and discreet inflammatory infiltrate (erythrocyte, neutrophil and rare lymphocytes)
3	Mild erosion of the endothelium and mild inflammatory infiltrate
4	Mild erosion of the endothelium with hemorrhage and discreet inflammatory infiltrate
5	Mild erosion of the endothelium and mild inflammatory infiltrate
6	Mild erosion of the endothelium and mild inflammatory infiltrate
7	Mild erosion of the endothelium and mild inflammatory infiltrate

Table 2. Shows the most frequent histological alteration that was found in rabbits of the **group B**.

Group B	Histological alterations (90 days of catheterization)
1	Extensive erosion, hemorrhage, mild inflammatory infiltrate
2	Mild erosion of the endothelium with mild inflammatory infiltrate
3	Mild erosion of the endothelium with mild inflammatory infiltrate
4	Mild erosion in the vein endothelium with thrombosis in adjacent artery
5	Mild erosion of the endothelium with mild inflammatory infiltrate
6	Extensive erosion of the endothelium with mild inflammatory infiltrate

Table 1 shows that 4 animals of **group A** (57%) presented mild endothelium erosion and mild or moderate inflammatory infiltrate, while other 2 animals of the same group presented endothelium extensive erosion (28%), and hemorrhage was observed in only one of the animals (14%).

Table 2 shows that only 3 animals (50%) presented mild erosion of the endothelium and mild inflammatory infiltrate, while endothelium extensive erosion and mild inflammatory infiltrate was observed in 2 animals (30%). One animal presented endothelium hemorrhage (16%) and, thrombosis (16%) was observed in a vessel, an adjacent artery, in another animal.

Fisher's Exact Test [20] was used to carry out statistical analysis to compare **groups A** and **B** with regards to the presence of histological alterations after phlebotomy (**Table 3**). Notwithstanding, the test didn't show significant statistical differences between both groups regarding inflammatory reactions percentage frequency (**$p = 0.65$**), but with a trend to show that it could have a significant statistical differences according we increase the number of animals, but we were restricted due this study was done in the graduation level.

4. Discussion

Central venous access especially in neonates is widely used in neonatal and pediatric intensive care units for infusions of total parenteral nutrition, antibiotics, and also several surgical procedures [2]. Studies have been carried out to determine if the children clinical conditions, nursing care or catheter type would have any effect in the catheter permanence time and its complications [4].

The presence of the catheter in contact with the vascular wall is the main cause of endothelial lesion with the formation of coagulation site and thrombosis (**Figure 5**) by deposition of a fibrin layer and other plasmatic proteins [14] [19]. It seems that the catheter introduced in the vein is initially recognized as a foreign object that is rapidly covered with fibrin and plasmatic proteins followed by platelets deposition that forms a thrombus on the catheter surface [19].

According to Vesely TM, 2003, a number of materials have been used to manufacture catheters such as Teflon® or PTFE that are widely known as thrombogenic, whereas silicone catheters are biologically inert and less susceptible to venous thrombosis [19]. Notwithstanding, in this study PTFE 17 GA catheters were utilized given that the study objective was to enhance the vascular and perivascular inflammatory effects [21].

RjV was chosen for venous dissection in the present study because it's easy to find in the neck and due to Vesely TM 2003 study that proves that vascular lesions and consequent thrombosis occur most frequently in patients whose catheterization was performed at the left side due to the presence of the brachycephalic trunk [19].

Table 3. Shows statistical analysis to compare **groups A** and **B** with regards to the presence of histological alterations after phlebotomy with no significant statistical differences between both groups (**p = 0.65**).

Group	Inflammatory reaction			
	Mild	Extensive	Total	%
A	5	2	7	28.6
B	4	2	6	33.3
Total	9	4	13	30.8

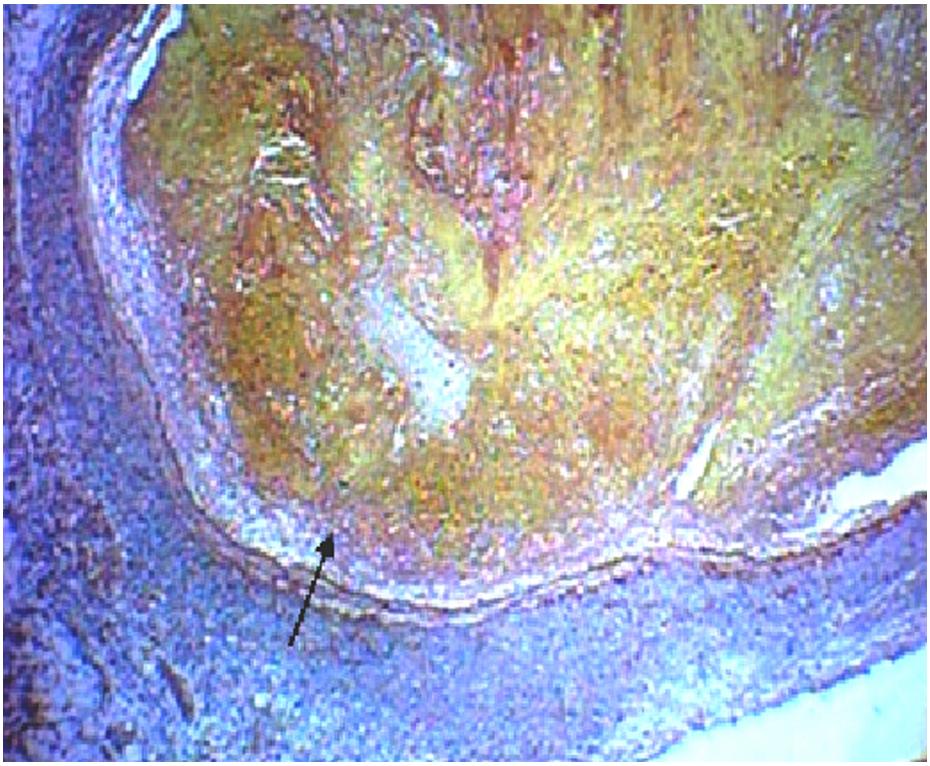

Figure 5. Shows a thrombusby deposition of a fibrin layer and other plasmatic proteins,wich blocks all the intraluminal space of the vein (arrow), in a rabbit of the **group B** (90 *days of catheterization*), with orcein stain, size 40×.

Several complications have been described, not only at the moment of the catheter insertion procedure, but also during the time of its permanence in the vein [5]. Lesions such as venous laceration, dissection of its walls and accidental arterial puncture, hematoma and even death were described as complications at the moment the catheter is inserted [6] [7]. Mechanical complications have also been described after intravascular catheter insertion, such as catheter displacement or disconnection; extravasation or infiltration of the infusion liquid; broken catheter and even artery occlusion, as it occurred with one of our animals that presented thrombosis of the adjacent artery [22]. In the present study, there were no vascular nor perivascular lesions such as hemorrhage, extravasation or local infiltrations, nor catheter breakage at the moment of its insertion or during its permanence in any of the study groups.

The two groups that presented endothelial lesion in this study started coagulation chain reactions by subendothelial tissue exposure, release of tumoral necrosis factor and interleukin-1, and toxins released due to necrosis or tissual lesion that was observed as mild or extensive erosion in the endothelium and inflammatory infiltrate [8]. However, this endothelial lesion did not worsen with time in the animals of **group B** whose catheter permanence time was of 90 days. Furthermore, their lesions were quite similar to those observed in the animals of **group A** whose catheter permanence time was only 15 days.

This may imply that if perivascular and particularly vascular inflammatory reaction (endothelial erosion) were

initially circumvented in order to avoid endothelial erosion and consequent vessel thrombosis, its effects could decrease through time or stabilize. The latter would allow a longer catheter permanence time, as the fully implantable catheters that can remain inserted in the body for more than 150 days [19].

5. Conclusion

We conclude that the lack of experimental models that would allow the study of vascular and perivascular inflammatory reactions hinders the study of these lesions. Moreover, this experimental model has proven to be adequate to demonstrate vascular and perivascular histological alterations that are common in the daily medical practice. The lesion in the veins in which the catheters remained for a longer time (**group B**) were not as bad as the lesions developed in the veins that were exposed to the catheter in a shorter period of time (**group A**). Studies regarding possible treatments for inflammatory lesions and thrombosis should be implemented to minimize the effects of lesions and allow a longer catheter standing time.

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