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Arguments to Apply Epinephrine for Pocket Hematoma Reduction. The MAITRE Study

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Abstract

Pocket hematoma (PH) is a common complication of implantations of cardiac electrophysiological devices with occurring at a particularly high rate in patients on oral anticoagulation or antiplatelet treatment. Different pharmacological agents with hemostatic effect are used to avoid PH. We supposed that the vasoconstrictor effects of epinephrine may reduce bleeding extent and be effective in prevention of PH. Maitre is the first clinical trial conducted with an aim to show the safety and efficacy of epinephrine in PH prophylaxis. We randomized 133 patients to receive either epinephrine or saline solution, which were added to a local anesthetic administered during pacemaker implantation. In cases of diffuse bleeding a method of pocket drainage was effectively used. Results showed that risk of PH was significantly higher in the group receiving epinephrine. We conclude that a local epinephrine effect may lead to a false impression of adequate hemostasis and force a surgeon to refuse from drainage insertion.

Introduction

Pocket hematoma (PH) is a known complication of pacemaker implantation procedure. PH is followed by local discomfort related to infiltration of hypodermic tissue.¹ In some cases it may demand surgical revision which increases a risk of device-related infection and prolongs hospitalization.^{2, 3} The results of conducted research indicate different PH rates. Makeev et al. (1999) according to the analysis of 700 implantation procedures concluded that it's a rare complication with a rate of 0.5%.⁴ European authors usually point out a higher PH rate reaching a value of 5%.⁵

Known risk factors of PH include procedure type (primary implantation or redo procedure), operator experience,⁶ size of implanting device, site of pocket formation, number of implanting leads, venous access type (subclavian or cephalic access).⁷ Moreover a risk of PH is connected with patient's medications. It has been shown that anticoagulation (AC) therapy significantly increases PH rate to 3.5%-16%.⁸ Chen et al. carried out a retrospective analysis of 1093 implantations of different devices and showed that double antiplatelet (AP) therapy, bridging anticoagulation and even moderate thrombocytopenia considerably increased the risk of PH.⁹

Key Words:

Epinephrine, Electrophysiological, Pocket Hematoma, Dual Antiplatelet.

Disclosures: None.

Corresponding Author: Nikolay Ilov. 414024 N. Ostrovskogo, 46-25, Astrakhan, Russia. A question of PH prophylaxis is relevant for patients with constant administration of AC and/or AP therapy. It's often suggested to perform pacemaker surgeries with partial or full interruption of these drugs.¹⁰ Our opinion is that in most cases it may bear a potential danger for patient health. It may be especially harmful after valve replacement surgery and PCI.

It is considered that careful surgical technique, earlier pocket formation,¹¹ electrocautery use and cephalic access may decrease the risk of PH.¹² Some centers recommend drain insertion into the device pocket,¹³ and different pharmacological agents with hemostatic effect are used to avoid PH.¹⁴ Epinephrine is one such drug. Vasoconstrictor effects caused by alpha-adrenoreceptors localized in the skin, mucous membranes and bodily organs are thought to strengthen potential and reduce bleeding extent. These advantages of epinephrine are widely and effectively used in ophthalmologic and stomatologic practice and may be useful during implantations of electrophysiological devices (EPDs). We couldn't find any publications devoted to this topic. Lack of clinical trials and evidence-based recommendations has led us to conduct this trial.

Materials And Methods

Maitre is a single-centered, double blind, randomized, placebocontrolled trial in two parallel groups of patients with indications for primary pacemaker implantation. The aim of our study was to study the safety of epinephrine's systemic and local effects and to estimate its influence on pocket hematoma prophylaxis.

The study protocol was approved by the Ethic Committee of Federal Centre for Cardiovascular Surgery (Astrakhan, Russia). We enrolled 133 patients who met inclusion and exclusion criteria (Table 1).

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria			
• a signed informed consent for participation in the study	 individual epinephrine and/or lidocaine intolerance 			
	known contraindications for studied drugs administration			
	- severe arterial hypertension: SBP \ge 200 mm Hg and/or DBP \ge 110 mm Hg			
	unstable IHD			
• men and women aged from 40 to 70 with indications for single and dual-chamber pacemaker	disturbances in any hemostasis mechanisms: number of thrombocytes, PT, fibrinogen, INR, tourniquet test;			
	• LV EF (Simpson) <35%			
	pregnancy and lactation			
	\bullet chronic kidney insufficiency: creatinine level higher than 110 $$ icromoles per liter $$			

Randomization

The type of solution (saline or epinephrine) as well as the name of the operator were previously coded in numbers. Generated using Excel random number generation functions. The patients were randomized in group A (75 patients) or in group B (58 patients). In spite of quantitative difference in the number of patients assigned to each group, the formed groups were comparable on main clinical and demographic characteristics (Table 2). According to the results of randomization a medical nurse added a 0.4% solution of epinephrine for group A or a saline solution (placebo) for group B to a local anesthetic (usually lidocaine). The operator therefore had no knowledge about anesthetic solution contents. A registration card was started for each patient.

Pacemaker Implantation Technique

A patient was administered a 1.0 gr cephazolin solution I/V before a procedure. A choice of implanting pacemaker type (single or dual-chamber) was made according to the Russian National Recommendations for performing of electrophysiological, catheter procedures and implanting EPDs (2013). The procedure was performed under the local anesthesia using a commonly accepted standard with pacemaker implantation in the right or in the left subclavian area. Moderate sedation wasn't administered. The choice of pocket location, venous access, lead fixation type and pacemaker mode was made by a surgeon depending on a specific case. Cephalic access and subcutaneous pacemaker placement were preferable. Electrocautery was routinely used in all implantations. Drainage was



Table 2: Clinical and demographic characteristics of studied patients

	Group A (Epinephrine)	Group B (Saline Solution)	P-value
Number of patients	75	58	p > 0,1
male/female	43/32 (57%/43%)	29/29 (50%/50%)	p > 0,1
Average Age	60 (55;65)	62 (56; 65)	p > 0,1
BMI	29,2 (26,4; 33,1)	30,7 (26,8; 34,7)	p > 0,1
Diabetes mellitus	5 (7%)	6 (10%)	p > 0,1
LV EF Simpson, %	58 (53; 61)	58 (53; 60)	p > 0,1
AP treatment	12 (16%)	8 (14%)	p > 0,1
AC treatment	22 (29%)	22 (38%)	p > 0,1
AP + AC treatment	2 (3%)	1 (2%)	p > 0,1
Without AC/AP treatment	39 (52%)	27 (47%)	p > 0,1

used in case of diffuse bleeding.

Patients Follow-Up

A 1 day bed rest and a 2-hour cold and compression therapy were prescribed for all patients. Patients didn't receive bridging anticoagulation and we didn't stop AP and/or AC therapy before and after pacemaker surgery. It was forbidden to administer any hemostatic drugs for the first two days after implantation. Antibiotics continued in case of severe bleeding from the device pocket and necessity to coutinue drainage.

Study Endpoints

Primary Endpoint: PH which was identified after two physicians' investigation by palpated infiltration, smoothing the pacemaker contour. PH was also assessed by ultrasound study routinely performed for all patients on the 3rd-5th day after implantation.

Secondary Endpoints: Death from any cause, cerebral vascular events, bleeding, pericarditis, tamponade, infectious complications, drainage insertion during the procedure, drainage prolongation, hospital stay days.

After an implantation procedure with blind use of epinephrine or saline solution a surgeon was asked to guess the used solution thereby giving a subjective evaluation of the bleeding extent.

Early End Of Study

The study could come to an early end for a patient in case of his/



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Table 3: Operative details

	Group A	Group B	Р
Single-chamber pacemaker	23 (31%)	19 (34%)	p > 0,1
Dual-chamber pacemaker	52 (69%)	39 (66%)	p > 0,1
Subcutaneous device pocket	62 (83%)	54 (93%)	p > 0,1
Subfascial device pocket	10 (13%)	4 (7%)	p > 0,1
Subpectoral device pocket	3 (4%)	0	p > 0,1
Cephalic venous access	29 (39%)	38 (66%)	p > 0,1
Subclavian venous access	41 (55%)	18 (31%)	p > 0,1
Cephalic + subclavian venous access	5 (6%)	2 (3%)	p > 0,1

her refusal to participate; according to the decision of a researcher in case of violation of the study protocol or non-related to PH need to perform surgical revision.

Statistical Analysis

Module Statistica 7,0 (Statsoft) was used to carry out a statistical analysis. Central tendencies were described as Median (IQR 25%; 75%). Data comparison and association analysis were provided by nonparametric methods with the p-value of 0.05 designated as the threshold for statistical significance.

Results

We randomized 133 patients who met the inclusion criteria. Average procedure time was 38 (35; 60) min. Both groups were comparable on gender, age and clinical features as well as on heart failure status and AP/AC administration (Table 3). Patients were discharged from hospital on the 5th (4; 5) day. All of them were recommended to communicate immediately with a surgeon in case of any skin changes at the site of the device pocket.

Three patients (2 from group A and 1 from group B) stopped a trial early due to necessity of surgical revision (lead dislodgement diagnosed three days after implantation).

Primary Endpoint

We observed primary endpoint (PH) in 7 cases, 6 of them occurred in group A (86%). PH risk was 0.09 (9%) in group A and 0.02 (2%) in group B (OR = 5,95%; CI: 2.1-7.3, p=0.003). Anesthetic solution content was the only significant difference in the characteristics of these patients (Table 4).

Secondary Endpoints

Lead dislodgement was observed in 5 patients (4%) and demanded surgical revision within the first three days (3 patients) or later (2 patients). Pneumothorax following pleural draining was registered in 2 patients. These complications had an equal rate in both groups (p>0.1).

A drain was inserted in 43 procedures (32%), 25% of them in group A and 44% - in group B (p=0.04). Pocket drainage duration didn't exceed 2 days and was on average 1 day in both groups (p>0.05).

There was no significant difference in length of hospital stay (5 (4; 5) days in group A and 5 (4; 6) days in group B, p=0.3). This parameter increased in case of PH reaching a value of 6 (5; 6) days. A positive correlation between the number of hospital stay days and any complication occurrence was observed (r = 0.18 при p=0.04), in case of PH it was also significant (r = 0.24, p=0.04). Other secondary endpoints didn't occur.

Discussion

What is PH?

The fact is that we have no common definition of PH. There is no doubt that this fact complicates the analysis of data from different

Table 4: Characteristics of the patients with PH								
Patients	1	2	3	4	5	6	7	
Study Group	А	в	А	А	А	А	А	
Age	64	64	64	66	64	57	69	
Gender	male	female	male	male	male	male	male	
BMI	34,5	27,2	28,4	21,6	42,9	31,7	34,1	
AP/AC treatment	-	AC	AC	AC	-	AC	AC	
Pacemaker type*	DCh	DCh	SCh	DCh	DCh	SCh	SCh	
Site of device pocket**	SC	SC	SF	SC	SC	SC	SC	
Venous access***	с	s	С	s	s	s	с	

studies.¹⁵ Niederhuber J. E. (2012) suggested that PH is a palpable swelling of the device pocket exceeding the size of implanted EPD. It was recommended to refer to ultrasound investigation in a disputable case.¹⁶ The primary point of BRUISE CONTROL (the Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial, 2013) was "clinically significant" PH which the researchers defined as PH demanding surgical reoperation with prolongation of hospitalization or interruption of oral ACs.⁸ These signs are found to be significant by other authors.¹²

In our trial the vast majority of PHs (6 of 7 patients) didn't demand active surgical strategy which corresponds to the published data.^{8,12} No doubt a necessity to perform reoperation has to be evaluated with a risk of infectious complications taken into consideration.¹⁷ Either insufficient reduction of PH size or PH expansion with the symptom of local tenderness are widespread criteria for such a strategy.¹⁸ We observed similar manifestations in one case with subsequent pocket puncture and evacuation of its liquid content.

The hospital stay in our study (5 days) seems to be too long for US and Europe but it's common in Russia. Our study demonstrated an increased number of hospital stay days in cases of PH which was supported by the statistical analysis (Figure 1).

In this randomized trial we evaluated the safety of epinephrine used as a component of local anesthesia and estimated its influence on PH prophylaxis. We showed that PH is a rare complication with rate of about 5%. Analyzing the characteristics of patients with PH participating in our study we found that these were older than those who didn't have PH (64 (64; 66) years vs 60 (54; 64) years old (Mann-Whitney U-test: U[7; 123]= 233.5; p=0.042). The results of correlation analysis prove the role of age in PH occurrence rate (r=0.18 при p=0.04). The possible explanation of this is a positive correlation between patient age and AC or dual AC+AP therapy administration (r=0.22 при p=0.04) - Figure 2.

Five of seven PH (71%) were registered in our trial in patients with AC administered before implantation. PH risk in this group was tripled compared to those who didn't receive any anti-clotting agents (10.6% vs 3%, p=0.04). It has been shown that AC and AP administration is one of the main causes of PH after pacemaker surgery. Kutinsky I.B. et al (2014) showed a high range of PH rate (11.1% and 24.2% at AP mono and dual therapy, 6.9% at AC therapy).¹² No patient taking AP agents had PH in our trial. It may be explained by drainage insertion in almost half of the implantation procedures performed for this group of patients.

In fact, there is no consensus about drainage use with pacemaker implantation. One of the arguments against such approach is a probable increasing risk of pocket infection (PI) after pacemaker

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surgery. Meanwhile about 4500 EPDs have been implanted in our center. A strategy to insert drainage in case of diffuse bleeding has been used for all these procedures with a total draining time no more than 3 days along with antibiotic administration for this period. We do believe that pocket draining has to be used especially in cases of subfascial or subpectoral pocket localization, which has been shown in this trial (r = 0.28 при р = 0.03). The PI rate in our center is annually about 0.4% and we didn't observe any correlation between drainage insertion and post implantation infection.

Influence Of Epinephrine On PH Prophylaxis

Our trial showed that use of epinephrine as a component of local anesthetic solution is safe during pacemaker surgery. We didn't observe any systemic effects of epinephrine with respect to blood pressure or heart rate increasing. In 3 cases we observed circular skin paleness above the pacemaker pocket which resolved in 2 or 3 days (Figure 3). We estimated it as a local vasopressor effect of epinephrine.

In spite of our expectations our trial didn't prove a positive influence of epinephrine on PH prophylaxis. A risk of PH was statistically higher in group A, in most cases of registered PHs drainage wasn't performed (in 5 from 7 patients, 71%). These were patients from group A and a surgeon's decision to refuse drainage was made due to lack of diffuse bleeding during implantation. Drainage was used in almost half of all the procedures in group B (44%) and in a quarter of implantations in group A (p=0.04) – Figure 4.

Local vasopressor effect of epinephrine were consistent with results of a surgeon poll a surgeon poll after the procedure. Surgeons correctly pointed out the patient group in 78% of implantations. We consider that a local epinephrine effect may lead to a false impression of an adequate hemostasis and provide false reassurance regarding the potential need for drain placement. It may explain a higher rate of PH in group A.

Patients Follow-Up

The studied patients had follow-up at 3, 6, 12 and 18 months after implantation. They were informed about necessity to contact a surgeon in cases of any pocket or wound compromise. We have observed no PI even in patients with PHs. There wasn't any necessity to perform reoperation for them. **Study Limitations**

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Figure 4: Secondary End-point - Pocket draining duration, n=43 (32%)

The evidence level of this trial is limited by the number of patients and single center participation.

Conclusions

Epinephrine administration as a component of local anesthetic solution during pacemaker implantation is safe and doesn't lead to any serious adverse effects. Meanwhile it doesn't decrease the risk of PH formation which is probably connected with local vasopressor epinephrine effects and delayed capillary bleeding in device pocket. The efficacy of pocket drainage in cases of diffuse bleeding has to be evaluated in future randomized trials.

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