

THE ROLE OF XANTHINOL NICOTINATE WITH HEPARIN AND DEXTRAN-40 IN POST TRAUMATIC ARTERIAL REPAIR CASES WHERE IMMEDIATE DISTAL PULSATION IS ABSENT: A PROSPECTIVE STUDY IN 150 CASES PRESENTING MORE THAN 10 HOURS POST INJURY

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HOW TO CITE THIS ARTICLE:

Lukram Sidartha, Mohit Sharma, Sunil Dixit, Anil Sharma. "The Role of Xanthinol Nicotinate with Heparin and Dextran-40 in Post Traumatic Arterial Repair Cases where Immediate Distal Pulsation is absent: A Prospective Study in 150 Cases Presenting More than 10 Hours Post Injury". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 38, August 25; Page: 9837-9846, DOI: 10.14260/jemds/2014/3274

ABSTRACT: OBJECTIVE: The therapeutic role of Xanthinol nicotinate along with Heparin and Dextran-40 was studied in the management of 150 patients in whom distal pulsations were not felt immediately post arterial repair surgery. **METHODS:** This is a prospective study of 150 patients who underwent arterial repair surgery in the Department of Cardiothoracic & Vascular Surgery, Sawai Man Singh Medical College, Jaipur, Rajasthan. Such of those patients whose distal pulsations were not palpable immediately after the arterial repair surgery were chosen in this study. **RESULTS:** Data is checked for completeness, consistency, and analysed using SPSS version 16.0. Descriptive statistics like mean, proportion etc. were used. Road traffic accident (61.3%) was the major cause of arterial trauma, post orthopaedic procedure contributing only 2% of the arterial injury. Upper limb injury with trauma to radial and ulnar arteries (30%) is the commonest. Most of the patients presented with warm limbs and intact motor sensory power (37.5%). Frank bleeding with complete arterial transection was seen in 66 patients (44%). 58 patients (38.7%) had reusable limb post the infusion therapy. 35 cases (23.3%) ultimately went to amputation due to development of gangrene subsequently. **CONCLUSION:** Preoperatively, the time interval from injury to diagnosis by the vascular surgeon is very crucial in restoring the integrity of the vessel. The golden period of intervention is up to 8 hours post injury. Associated orthopaedic traumas (bone fractures) delays the primary arterial repair surgery. Combined infusion therapy of Dextran-40, Unfractionated Heparin and Xanthinol nicotinate was found effective in postoperative cases of arterial surgery where distal artery pulsation was not palpable.

KEYWORDS: Xanthinol nicotinate, Heparin, Dextran-40, Arterial trauma, Vascular anastomosis.

INTRODUCTION: Road traffic accident (RTA) has become a major public health hazard in our country. It comprises the majority of vascular injury cases brought to the Emergency ward. Besides RTA, other causes of vascular injury include assault, animal bite and post cannulation. From ancient times, where war injuries were the main causes of vascular injury, till today, vascular injury repair and limb salvage surgery pose a main challenge to the vascular surgeons.

Late nature of presentation with motor-sensory loss and skin colour changes coupled with difficulty in identification of vascular anatomy following extensive soft tissue injuries have made the job of the vascular surgeons all the more demanding. Apart from the intra-operative anastomosis, non-appearance of pulsation of peripheral vessels and infection are major concerns for the surgical team during the immediate post-operative period.

ORIGINAL ARTICLE

With computer tomography angiography, arterial injuries are accurately diagnosed with proper clinical assessment. Well-equipped specialized trauma centres have helped in reducing the time for preparation of surgery. Following the operations if the distal vessel pulsates, it gives the surgeon the assurance of a successful repair. Following a technically satisfactory vascular repair and detection of intra-operative pulsation, in the immediate post-operative period, more often than not, distal pulsations are absent.

In the present study, we evaluate the action of the infusion of Xanthinol nicotinate along with Heparin and Dextran-40 in the post-operative period as an anticoagulant where immediate pulsation is absent vis-a-vis the benefits or otherwise of the infusion therapy to the patient.

AIM: The infusion of Xanthinol nicotinate, Dextran-40 and unfractionated Heparin are used to reduce the post-operative thrombosis and oedema following arterial anastomosis – in patients where pulsations fail to return immediately.

MATERIAL AND METHODS:

Study Design: This is a prospective study for a period of 24 months from August 2012 to July 2014 of 150 patients treated in the Cardiothoracic and Vascular Surgery Department of SMS Medical College, Jaipur, Rajasthan. The study is based on post-operative clinical observation and patient response following the infusion of a combination of Xanthinol nicotinate, Dextran-40 and Heparin.

Study Group: 150 patients in whom distal peripheral pulses fail to appear immediately following vascular anastomoses were included in the study group; all the patients were treated in the Department of CTVS, SMS Medical College, Jaipur, Rajasthan.

Exclusion Criteria: Patients whose peripheral arteries were normal and pulsating after the arterial anastomosis are not included in this study.

Data Collection: Relevant data from a well-designed proforma was evaluated and analysed to obtain the results of this study.

Statistical Analysis: Data is checked for completeness, consistency and analysed using SPSS Version 16.0. Descriptive statistics like mean, proportions etc. were used.

In the present study, we select a group of patients on whom vascular repair surgery have been performed and in immediate post-operative period there is no distal pulsation of the limbs despite a successful anastomosis. This is a prospective study and has been done in the Vascular Surgery Department of SMS Hospital, Jaipur.

In a preliminary trial, Xanthinol nicotinate helped a significant number of patients whose peripheral obliterative vascular disease had been resistant to previous treatment (Davis and Rozov, 1973).¹ Musil (1973) among others also reported encouraging results with this preparation.²

Hence, Xanthinol nicotinate which has a potent action on peripheral circulation³ was chosen in order to assess its potent therapeutic role in helping patients with post-operative absent pulsation.

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Both low dose Heparin and Dextran-40 have been proven to prevent post-operative thrombosis. Here we evaluate the effects of low dose Heparin and Dextran-40 along with Xanthinol nicotinate in post-operative arterial repair.

Patient Population: After proper clinical evaluation and resuscitation of the patient in the Emergency trauma ward and proper documentation with Computer Tomography Angiography whenever required, patients are taken for vascular repair with adequate arrangement for blood transfusion. Post operatively, if immediate distal pulsations are absent, patients are selected for observation for this study.

Drugs, Dosage and Route of Administration:

Dextran-40: It is low molecular weight glucose polymer plasma expander containing dextran $(C_6H_{10}O_5)_n$ of 40,000 dalton molecular weight. It is produced from cane or beet sugar by the action of bacterium *leuconostoc mesenteroids* B512.

It is most frequently used to restore blood volume in hypovolemic patients. In addition, it may exert favourable effects on the microcirculation by decreasing blood viscosity. It also decreases rouleau formation, leukocyte adhesiveness to endothelial cells and also decreases serum fibrinogen and clotting factors. It firmly adheres to circulating RBCs *in vivo*.

It also attaches itself to arterial walls, which have been damaged by physical rather than chemical bonding. This molecular coating may sterically prevent the critical concentration of substances necessary for clotting or may insulate or counter transmural thrombogenic potentials. Due to all this Dextran-40 possesses thromboprophylactic properties.⁴

In vivo it has been shown to be an effective plasma expander that lowers blood viscosity and increases peripheral blood flow.^{5,6} In addition, it has been shown to inhibit platelet adhesion and to specifically interfere with the interaction of factor VIII, platelets, and endothelial cells.^{7,8}

Heparin: Heparin was discovered by McLean⁹ in 1916, and Brinkhous and associates¹⁰ demonstrated that its anticoagulant effect requires a plasma cofactor later named antithrombin III (AT-III)¹¹ but is now known simply as antithrombin (AT). Rosenberg and Lam,¹² Rosenberg and Bauer,¹³ and Lindahl et al¹⁴ elucidated the mechanisms responsible for the heparin/AT interaction.

Xanthinol Nicotinate: Xanthinol nicotinate belongs to category of theophylline drug¹⁵. It enhances blood flow to the peripheral and cerebral tissues¹⁶. Xanthinol nicotinate augments the glucose and oxygen utilization in the cells; and checks the rise in serum lipids and fibrinogen levels.¹⁷ It is a combination of Xanthinol and Niacin.

Technique of Vascular Anastomosis: Anticoagulation is started intra-operatively once the affected part of the artery is exposed and repair is initiated. Unfractionated Heparin is used and is administered in bolus injection as per body weight. Anastomosis is started once the heparin starts acting i.e. 5 minutes after administration.

Heparin is repeated as per the length of the time of surgery. Post anastomosis, bolus dosage of soda bicarbonate is injected to prevent acute renal injury due to the toxins. Post soda bicarbonate injection, the arterial clamps are released and distal flow and pulsations are checked.

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After proper hemostasis and cleansing, the wound is closed. After successful vascular repair if the distal peripheral pulsations are absent then the subject is picked up for this study.

Infusion Technique and Monitoring: 500ml of Dextran- 40+25000 IU unfractionated Heparin +10 ampoules of Xanthinol nicotinate(6000mg) is infused in peripheral vein continuously by a microdrip set @30 microdrops per minute. APTT is measured every 6th hourly to fix the APTT at 3 times the normal value.

OBSERVATION AND RESULTS: Successful outcome in vascular trauma depends on early diagnosis and early referral to the specialists. In our set up majority of the patients presented beyond what is considered as the “Golden Period”. The time interval between beginning of the trauma and arrival to our centre was a mean of 10 hrs. However diagnosis of the vascular injury was done as soon as the patient reached the Emergency, by assessing the peripheral circulation with the assistance of hand Doppler and physical examination.

Our assessments post-operatively depend entirely on clinical observation and patient response. The following features are used to evaluate the response to Dextran-40 +Heparin + Xanthinol nicotinate infusion: 1) Skin temperature, 2) Reversal of cyanotic skin colour, 3) Capillary filling, 4) Motor–Sensory power, 5) Reappearance of pulse/positive on pulse oscillometry.

Observation Period: 12 days or till the wound heals and oral anticoagulation starts acting with an INR of 2-3.

Age	N	%
10-20	13	8.6
21-30	48	32
31-40	28	18.6
41-50	30	20
51-60	0	0
61-70	18	12
71-80	13	8.6
>81	0	0

Table 1: Age Incidence

The incidence was maximum in 21-30 years of age followed by 41-50 year age group.

	N	%
Age	39.1 + 18.3	
Male	103	
Female	47	68.7%
Weight	61.4 + 4.6	31.3%
BMI	22.6 + 3.1	

Table 2: Baseline demographic characters

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Continuous data or variable are expressed as mean + SD. Categorical data are expressed in numbers. The mean age of patients (n=150) in this study is 39.1 with standard deviation of 18.3. Incidence is more in males with 68.7 % and less in females with 31.3%.

Nature of trauma	n (%)
Road traffic accident	92 (61.3)
Assault	35 (23.3)
Animal bite	16 (10.7)
Post cannulation	4 (2.7)
Post-orthopadic procedure	3 (2.0)

Table 3: Trauma History

Maximum incidence is road traffic accident comprising 61.3% followed by assault (23.3%) and animal bite (10.7%). Iatrogenic complications like post-cannulation (2.7%) and post orthopaedic procedure injury (2%) comprising only a small part.

Site of involvement		n (%)
Upper Limb	Subclavian artery	8 (5.3)
	Axillary artery	12 (8.0)
	Brachial artery	23 (15.4)
	Radial/ulnarartery	45 (30.0)
Lower limb	Common iliac artery	0
	External iliac artery	2 (1.3)
	Femoral artery	24 (16.0)
	Popliteal artery	36 (24.0)

Table 4: Site of Vascular Injury

Upper limb injury is maximum with radial and ulnar artery comprising 30% while popliteal artery injury comprises 24%. Incidence of Injury to the major vessels are less with subclavian artery(5.3%) and external iliac artery (1.3%).

Condition of Limb	n (%)
Warm with motor sensory power	56 (37.5)
Cold with motor sensory power	34 (22.7)
Without motor sensory power	22 (21.3)
Pre-gangrenous changes	28 (18.7)

Table 5: Presentation

Although the time of presentation is more than 10 hours post injury, most of them presented with warm limbs with intact motor sensory power (37.5%).Cold limb with motor sensory power comprises 22.7%. But cold limbs without motor sensory power (21.3%) and pre gangrenous changes (18.7%) were relatively common in presentation.

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Type of wound	n (%)
Open wound	112 (74.7)
Closed wound	38 (25.3)

Table 6: Type of wound and arterial injury

Most of the wounds were open wound (74.7%) while only 25.3% presented with closed wound.

Type of arterial injury	n (%)
Artery transected	66 (44.0)
Artery contused only	84 (56.0)

Table 7: Mode of arterial injury

Frank bleeding with transected artery were 66(44%) in number while most of them presented with contused segment (56%).

Variable	Number of patients (n)
Skin Temperature improvement	80 (out of 150)
Reversal of Cyanotic changes	10 (out of 20)
Capillary filling improvement	70 (out of 150)
Motor-sensory improvement	60 (out of 110)
Re-appearance of distal pulsation	40 (out of 150)

Table 8: Patients showing improvements in signs and symptoms after infusion therapy

Out of the 150 patients 80 patients have skin temperature improvement post-infusion therapy. Reversal of cyanotic changes was found in 10 patients out of 20 patients. Pre-gangrenous changes and capillary filling was improved in 70 patients out of 150. There is motor sensory improvement in 60 patients out of 110 patients. Reappearance of distal pulsation is present in 40 out of the 150 patients.

Re-usability	n (%)
Limb normal	58 (38.7)
Limb survived but not usable	57 (38.0)
Limb ultimately amputated	35 (23.3)

Table 9: Re-use of limb post-surgery

In 58 patients (38.7%), the post operated limbs survived and can be used in normal day to day activities. Few of them complained of pain which cannot be explained medically. In 57 cases (38%) the limbs survived with well perfused distal parts but the motor sensory cannot be maintained properly. So they cannot be used for day to day function. 35 cases (23.3%) ultimately went to amputation on follow up due to gangrenous changes/infection or due to excessive pain with non-healing ulcer.

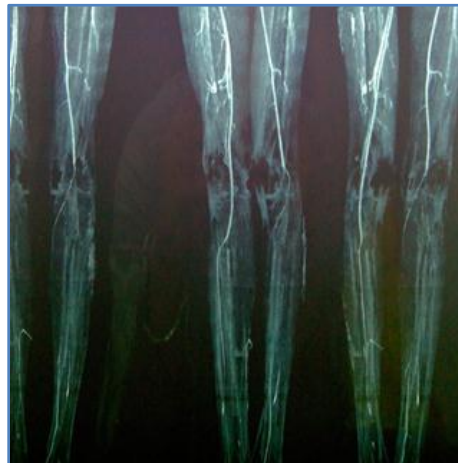


Fig. 1: Angiogram showing left popliteal block before operation

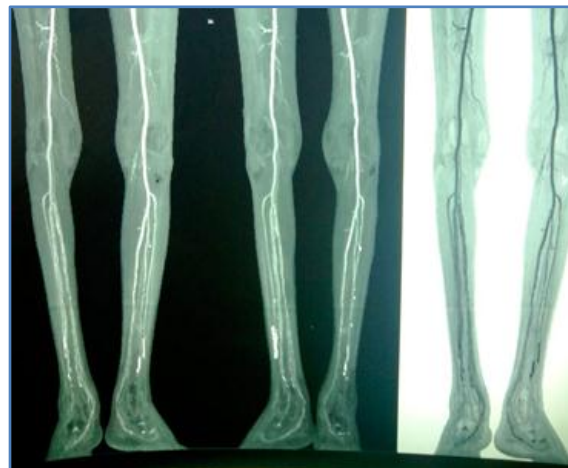


Fig. 2: Angiogram showing removal of left popliteal block after operation

SUMMARY: In our study a total of 150 patients were observed. Maximum incidence was found in 21-30 years of age group. The incidence was more in males comprising 103 patients with 68.7% and 47 females with 31.3%. On the nature of injury, road traffic accident had maximum incidence with 92 patients (61%) followed by assault 35 patients (23.3%). Iatrogenic procedures producing vessel injury by post cannulation is 2.7% and post orthopaedic procedure is 2%.

Upper limb injury is more common with radial or ulnar injury comprising 45 patients (30%). In lower limb injury popliteal artery injury is most common with 36 patients (24%). 56 patients (37.5%) presented with preserved motor and sensory power and warm limbs. 34 patients (22.7%) had cold limbs with preserved neural power while 22 patients (21.3%) presented with loss of neural power. Pregangrenous changes were found in 28 patients (18.7%). Most of the wounds were clean wounds with less contamination.

Open wounds were found in 112 patients (74.7%) and closed wounds in 38 patients (25.3%).

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Transected artery were found in 66 patients (44%) and only segment contusion was found in 84 patients (56%).

On observation of the post infusion changes, skin temperature is improved in 80 out of 150 patients while reversal of cyanotic changes were seen in 10 out of 20 patients. There is marked capillary improvement in 70 out of 150 patients. Increased motor sensory function is found in 60 out of 110 patients while re-appearance of distal pulsation is found in 40 out of 150 patients.

Overall 58 patients (38.7%) can use their limbs normally in day to day activities. But 57 patients (38%) had survived limb but sensory motor dysfunction was found. 35 patients ultimately went to amputation due to multiple factors.

DISCUSSION: In the Indian scenario losing a limb is still a taboo, people want to save their limbs whether it is usable or not and everyone wants to give a chance to surgery before amputation specially the younger victims. The main task of a vascular surgeon is not the surgery alone but the pre-operative and the post-operative care that occupy a major portion of management regime.

As most of the trauma centres are not properly equipped with vascular surgeons and the public are not aware of the seriousness of vascular injury, precious time is lost in the transit and referral of the patient. Many cases come with neurosensory loss and pre-gangrenous changes. The likely complications of vascular surgery of the patient going into acute renal failure and multi organ dysfunction after revascularization were explained. Most patients still do not give consent to an amputation and insist on giving a trial of surgery.

The golden period of intervention i.e. upto 8 hours post injury were mostly lapsed in our trauma scenario due to late arrival in the hospital giving rise to impaired neuro-sensations and gangrenous changes. Sometimes the patient presented with shock and bony fracture which needs to be corrected first losing some more precious time.

Apart from all the pre-operative problems faced by a vascular surgeon, the major challenge comes after anastomosis of the artery. Following a good clearance of the vessels by Fogarty balloon catheter, both distal and proximal segments, the most reliable sign is the presence of distal peripheral pulse.

But due to multifactorial reasons, immediately in the post-operative period, pulsation of the vessel after anastomosis ceases, and it becomes a major worry for the vascular surgical team. At this juncture, the role of anticoagulation infusion therapy comes into the picture.

Role of Heparin: The heparin-Anti thrombin complex inactivates a number of coagulation enzymes, including thrombin factor (IIa), factors Xa, IXa, XIa, and XIIa. Of these, thrombin and factor Xa are most responsive to inhibition, and human thrombin is about 10-fold more sensitive to inhibition by the heparin-AT complex than factor Xa.

It is now known that the active center serine of thrombin and other coagulation enzymes are inhibited by an arginine-reactive site on the AT molecule and that heparin binds to lysine site on AT, producing a conformational change at the arginine-reactive site that converts AT from a slow, progressive thrombin inhibitor to a very rapid inhibitor of thrombin and factor Xa.¹³

Role of Dextran-40: Dextran-40 is composed of long-chain carbohydrate polymers with a mean molecular weight of 40,000. Several studies have suggested that the administration of dextran 40

increased the early patency of infrainguinal bypass grafts.^{18,19} As a result, many surgeons began to use dextran as a routine adjunct to lower extremity arterial reconstruction.

Role of Xanthinol Nicotinate: Xanthinol nicotinate enhances blood flow to the peripheral and cerebral tissues⁶. It enhances microcirculation by decreasing platelet aggregation and increasing erythrocyte elasticity and thus improving the flow properties of blood.²⁰ It also possesses vasodilatory effect by decreasing the peripheral resistance of the vessels.²¹

Hence in our study we use a pharmacologically and functionally compatible combination of Xanthinol nicotinate, unfractionated Heparin and Dextran-40 infusion immediately post operatively.

This combined infusion therapy was found effective in postoperative cases of arterial surgery where distal artery pulsation was not palpable.

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Date of Submission: 09/08/2014.
Date of Peer Review: 11/08/2014.
Date of Acceptance: 20/08/2014.
Date of Publishing: 25/08/2014.