

# The Role of Anticoagulant Therapy with Heparine in Treatment of Acute Hand Ischemia

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*Hand ischaemia has multiple causes. The Methadone (C<sub>21</sub>H<sub>27</sub>NO) - opioid family of drugs and Alprazolam (C<sub>17</sub>H<sub>13</sub>Cl<sub>1</sub>N<sub>4</sub>) microcrystals, available under the trade name Xanax - benzodiazepine anxiolytic, when using in case of drugs abuser, are very powerful embolic agents which can cause thrombosis of small vessels. Microvascular embolization caused by microcrystals of the injectable powder has contributed to the process of ischaemia. This paper brings into discussions a case of acute ischaemia of the right hand due to intra-arterial injection of suspended tablets of Methadone and Alprazolam microcrystals into the right radial artery, in the distal 1/3 of the forearm. The therapeutic management consisted of restoring the arterial circulation at the ischaemic segment to prevent the propagation of thromboembolic complications by using of i.v. heparine and to preserve the function of the hand by preventing delayed ischaemia and compartment syndrome followed by necrosis. Heparin is a drug widely used in the treatment and prevention of arterial and venous thrombosis. The main effect of heparins lies in their anticoagulant activity. Heparins are involved in different pathways of the coagulation cascade with anticoagulant, antithrombotic, profibrinolytic, anti-aggregative, as well as anti-inflammatory effects. This paper aims to discuss a severe case of ischaemia which demonstrates that intra-arterial injection of oral drugs can lead to limb loss with currently accepted therapy.*

**Keywords:** Heparin, Methadone, Alprazolam, intraarterial injection in drug abuse, hand ischaemia

The World Health Organization estimates for 2014 that there are globally around 16 million people who use injectable drugs [1], which leads to a high incidence of accidental or intentional intraarterial injection in drug abuse. Lately, there has been an increased concern for the assessment of different therapies [2, 3], for the use of polymeric and composite materials in bone disorders [4] and also for reducing the effect of pollutants on the environment and human health [5-7].

The first cases of hand gangrene that are cited in medical literature go back to 1942, when the patient lost 3 fingers secondary to intra-arterial injection of thiopental, followed by 12 similar cases in 1948 [8].

The list of non-injectable substances includes crushed tablets or powder, liquid contents of capsules and solid gel preparations. The variety of drugs consist of a wide list of narcotic medication that includes: *codeine* (C<sub>18</sub>H<sub>21</sub>NO<sub>3</sub>), *zolpidem* (C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O), *ketamine* (C<sub>13</sub>H<sub>17</sub>NO), *temazepam* (C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub>), *thiopental* (C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S), *sodium pentobarbital* (C<sub>11</sub>H<sub>17</sub>N<sub>2</sub>NaO<sub>3</sub>), *sodium sulfobromophthalein* (C<sub>20</sub>H<sub>10</sub>Br<sub>4</sub>Na<sub>2</sub>O<sub>11</sub>S<sub>2</sub>), *meprobamate* (C<sub>9</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>), *methadone* (C<sub>21</sub>H<sub>27</sub>NO) and *alprazolam* (C<sub>17</sub>H<sub>13</sub>Cl<sub>1</sub>N<sub>4</sub>) microcrystals [8-10].

The most frequent sites of injection are the antecubital area; midbrachial area and the femoral area having as consequence ischaemia distally to the site of injection, tissue necrosis, infection, loss of function and amputation. Goldberg demonstrated in 1984 that the unique component of a codeine tablet which determines gangrene is the microcrystalline cellulose, while the injection of pure codeine is harmless [11, 12].

This paper presents the case of a 31 years old man ex-intravenous drug abuser (10 years ago) who for the past 6 years has been treated with Methadone (3-6 pills/day). The patient came to the emergency department 6 hours after

injecting himself into the radial artery with a suspension composed of 10 pills of *Methadone* (2.5 mg) and 4 pills of *Alprazolam* (Xanax 1 mg). The symptoms included: extreme pain, anxiety, *livedo reticularis* in the fingers, non-palpable pulse at the radial artery, very slow capillary refill at the apical region of the fingers. The diagnosis of *acute right hand ischaemia* was established after a Doppler ultrasound of the radial, ulnar and arterial arches of the hand. The medical treatment included: continuous anticoagulation therapy for 14 days, antispasmodic and anti-inflammatory drugs, as well as psychiatric drugs. Unfortunately, the necrosis started and continued until it reached the distal metacarpal level, resulting in amputation of all fingers of the right hand.

## Experimental part

The patient presented to the emergency room complaining of acute pain in the right hand. His symptoms included anxiety, tachycardia, intense perspiration, pallor.

Clinical examination revealed: pallor of the right hand, cold and cyanotic skin; absence of the capillary pulse, fingers held in a flexed position with hard and painful extension. In the 1/3 distal forearm region the skin was also pallor, delayed capillary refill, moderate edema and tenderness at the anterior forearm compartment.

Diagnostic evaluation must include manual (*Allen test*) and *Doppler ultrasound* - based examination of extremity pulses including palmar arch and digital pulses.

There was no pulse present at the radial artery, unlike the ulnar artery which had a pulse and wasn't affected. The *Allen test* showed an absence of arterial refill after radial artery decompression. A *Doppler ultrasound* was performed. It showed modifications of the arterial flow at the palmar arterial arches (*decreased flow*) and radial artery (*absent flow*).

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The patient was admitted into the *Department of Plastic and Reconstructive Surgery from Clinical Emergency Hospital Bucharest, Romania*, an immediately started with anticoagulation therapy, with an aPTT (*activated partial thromboplastin time* - a medical test that characterize blood coagulation) target between 60-70 s. The blood serology revealed leukocytosis ( $9.6 \times 10^3/\text{ul}$ ) and an important muscle ischemia: creatine kinases (*CK*) = 3439 U/L and creatine kinase-muscle/brain (*CK-MB*) = 154 U/L.

The patient was taken into the operative room (OR) and prepared for surgery. Under brachial plexus block anesthesia the following intervention is performed: decompression incision at the distal third of the right forearm and at the carpal tunnel, fasciotomy for the anterior compartment of the forearm [13]. A central arterial catheter was inserted in the left subclavicular artery for drug administration (heparin, antibiotics, antispasmodic and NonSteroidal Anti-Inflammatory Drug - NSAIDs), fluids and electrolytes were administrated along with hand immobilization and elevation of the superior right arm.

The second day post-injection the *CK* started to increase (5159 U/L), followed by progressive decrease, until normalization on the 17<sup>th</sup> day of admission. The patient's general state, mental status and local evolution were periodically assessed; among the followed parameters is the capillary pulse, the sensibility and mobility of the affected fingers and the ulnar pulse.

On the 25<sup>th</sup> day after admission, having normal blood tests, the second surgical intervention was performed: necrectomy for all fingers of the right hand and amputation of unhealthy tissue at the subcapital level of all metacarpals. During the surgery we noticed liquefied thenar muscles and non vascularised metacarpal diaphysis; all unhealthy tissue is debrided from the 2<sup>nd</sup> - 3<sup>rd</sup> - 4<sup>th</sup> inter-metacarpal space. The incision is sutured from the distal 1/3 of the forearm.

On the 46<sup>th</sup> day after admission, a second excision of the non- viable tissues was performed and the defect created was covered by harvesting a split-thickness skin graft (STSG) from the anterolateral part of the right thigh.

## Results and discussions

Intra-arterial injection among drug addicts becomes frequent when there are no more viable veins left for them to insert a needle. Even more dramatic is their attempts to inject crushed pills in peripheral arteries. The result may be reversible ischaemia, distal to the site of injection or, as in this case, necrosis and loss of body parts.

In this article it is presented a severe case of ischaemia which demonstrates that intra-arterial injection using oral drugs *Methadone* (2.5 mg) and *Alprazolam* (Xanax 1 mg) can lead to limb loss with currently accepted therapy.

The main symptoms that appear in the first hours after injection are the local ones, with intense pain, cyanosis, specific position of the finger- in flexion - and the absence of the radial pulse. They are followed by tissues modifications, knowing that among all the structures in the hand, the most sensible to ischaemia are the muscles, after which the process of rhabdomyolysis begins.

In our patient immediate drug treatment was initiated along with surgical intervention. The highest value of *CK* was recorded at 30 hours after intra-arterial injection (5159 U/L and it become normal in the 17<sup>th</sup> day after admission). The progression of the necrosis resulted in amputation from the subcapital level of the metacarpals II-V. The patient received psychiatric evaluation and medication according to his addiction. During admission positive feed-back was received from the patient, he was co-operating and there

were no notable incidences. The patient came to visit after discharge every 3 days for the next 2 weeks, during which time the suture material was removed and a hand prosthesis was recommended.

Ischaemia due to intra-arterial injection of non-dissolvable pills is not a frequent pathology, but it requires urgent medical attention. The most frequent place for injection described in literature is in the right radial artery [14-16], followed by the brachial artery, femoral artery and ulnar artery [17- 20].

The result from intra-arterial injected oral drugs may vary from regaining the permeability of the blood flow to minimum necrosis or even disarticulation at the wrist joint [21].

All five fingers of the right hand continued to develop necrosis, despite medical therapy with heparin, antispasmodic, anti-inflammatory, anti-aggregation and antibiotic drugs.

Surgery was performed in the first hours after arriving at the emergency room the goal being the decompression of the anterior compartment of the forearm and the carpal tunnel. The anticoagulants' role was to stop the process of thrombosis, taking into consideration that the palmar arches were obstructed and that the capillary refill time in the fingers was barely noticeable.

The particularity of the case consists in the presence of microemboli that cause ischaemia of the microcirculation from the level of the digital collateral arteries and the arteries for the intrinsic muscles of the hand, resulting in a high level of necrosis. In the end, the presence of granular tissue is a certainty that blood flow is established and that there is no dead tissue. In this case repeated excisions were performed, which latter allowed graft adhesion.

Another particularity of this case was the fact that the palmar arches remained viable after administration of anticoagulation therapy [22-24].

## Conclusions

In concordance with the majority of related literature, post-injection ischaemia using drugs like *Methadone* (2.5 mg) and *Alprazolam* (Xanax 1 mg) is most commonly seen at the right upper limb, especially due to easy access to the radial and ulnar arteries [25-27].

The development of ischaemia has multi-factorial origins and depends on: the site of the injection; the properties of the injected powder and the volume of the injected drug.

The progression of the ischaemia depends on the physiological reaction, which varies according to the vascular spasm, thrombosis and emboli derived from the non-solvable drugs.

The large number of cases of acute ischaemia of the upper limb is related to number drug addicts who have started injecting non-solvable pills in their arteries.

The onset of hand ischemia can be - as seen in our case report - delayed and the risk of pending limb loss may be missed upon initial presentation.

In this paper was describing the successful thrombolytic medical management of an ischemic hand using the continuously anticoagulation therapy for 14 days, antispasmodic and anti-inflammatory drugs therapy.

Anticoagulation therapy with *Heparin* were administered in order to reduce the effect of serious digital ischaemia. The anticoagulants' role was to stop the process of thrombosis, taking into consideration that the palmar arches were obstructed and that the capillary refill in the fingers was barely noticeable.

Additionally we recommend administration of

anticoagulation therapy to reduce the risk for thromboembolic complications.

The patient was followed-up for 1 month, until all skin defects were covered by granulation tissue and by epidemics advancement of the nearby skin. The remaining part of the hand can be substituted with silicon prosthesis.

## References

1. GOLDBERG, I., BAHAR, A., YOSIPOVITCH, Z., *Clin Orthop Relat Res.*, **188** (9), 1984, p. 223.
2. TRUTA, E., DAVIOIU, A.M., JINESCU, G., MITU, A.M., CARAGEA, G., IONICA, M., STANCIULESCU, E.L., *Rev. Chim. (Bucharest)*, **67**, no. 4, 2016, p. 609.
3. TUDOSIE, M.S., TRUTA, E., DAVIOIU, A.M., STANCIULESCU, L., JINESCU, G., MITU, A.M., FORJE, M., HORHOTA, L., BOJESCU, A.A., MARES, A.M., IONICĂ, M., *Rev. Chim. (Bucharest)*, **68**, no. 2, 2017, p.279.
4. PREDESCU, V., JINESCU, G., OLARU, R.I., PRESCURA, C., DELEANU, B., *Rev. Chim.(Bucharest)*, **67**, no. 8, 2016, p.1513.
5. JINESCU, V.V., MANEA, S-E, JINESCU, G., NICOLOF, V-I, *Rev. Chim.(Bucharest)*, **68**, no. 9, 2017, p.2189
6. JINESCU, V.V., TEODORESCU, N., JINESCU, G., PANAIT, I.C., *Rev. Chim. (Bucharest)*, **67**, no. 12, 2016, p.2607.
7. JINESCU, V.V., NICOLOF, V-I, JINESCU, G., ENACHESCU, G.L., *Rev. Chim. (Bucharest)*, **67**, no. 9, 2016, p.1673.
8. LLOYD W.K., PORTER J.M., LINDELL T.D., RÖSCH J., DOTTER C.T., *American Journal of Roentgenology (JAR)*, **117**(4), 1973, p.892.
9. STEPHEN, E., LANKENAU, SANDERSA B., BLOOMB, J., HATHAZIB, D., ALARCON, E., TORTUD, S., CLATTSE, M., *Drug Alcohol Depend.*, Ed. Elsevier, **87**(2-3), 2007, p.183.
10. BHABRA, S., MESHIKHES, A.N., THOMSON, G.J., CRAIG, P., PARROTT, N.R., *Eur J Vasc Surg*, **8**(2), 1994, p.240.
11. ENGLER, H.S., PURVIS, J.G., KANAVAGE, C.B., OGDEN, L.L., FREEMAN, R.A., MORETZ, W.H., *Arch Surg.*, **94**(5), 1967, p.644.
12. WOODBURN, K.R., MURIE, J.A., *British Journal of Surgery*, **83**(10), 1996, p.1329.
13. LASCAR, I., *Plastic surgery compendium*, chapter 16<sup>th</sup> - The compartment syndrome, Ed. Academiei Romane, 2009.
14. THALHAMMER, C., ASCHWANDEN, M., KLIEM, M., STÜRCHLER, M., JÄGER, K.A., *Dtsch Med Wochenschr.*, **129**(45), 2004, p.2405.
15. EBERT, F.W., *Handchir Mikrochir Plast Chir.*, **32**(3), 2000, p.197.
16. CORSER, G., MASEY, S., JACOB, G., KERNOFF, P., BROWNE, D., *Anaesthesia*, **40**(1), 1985, p.51.
17. BITTNER, C.H., ZUBER, M., EISNER, L., *Swiss Surg*, **8**(6), 2002, p.281.
18. HERING, J., ANGELKORT, B., *Dtsch Med Wochenschr.*, **131**(24), 2006, p.1377.
19. RADELEFF, B., STAMPFL, U., SOMMER, C.M., BELLEMANN, N., HYHLIK-DUERR, A., WEBER, M.A., BOECKLER, D., KAUCZOR, H.U., *Cardiovasc Intervent Radiol.*, **34**(5), 2011, p.1085.
20. PRATIKTO, T.H., STRUBEL, G., BIRO, F., KROGER, K., VASA, **33**(1), 2004, p.52.
21. SHUKLA PC, *J Emerg Medd.*, **13**(1), 1995, p.65.
22. CITRON, B. PHILIP, et al., *New England Journal of Medicine*, **283**(19), 1970, p.1003.
23. ROBERT D GALIANO, MCCARTHY JG (Ed.), GALIANO RD (Ed.), BOUTROS SG (Ed.), *Current Therapy in Plastic Surgery. Vascular Insufficiency and Ischemia*, 1<sup>st</sup> Ed., New York, Elsevier, WB Saunders, 2005.
24. TOR WO CHIU, TZE YEAN KONG, *Key Clinical Topics in Plastic & Reconstructive Surgery - Skin grafts*, Jp Medical Ltd Ed., 2014, 352 p.
25. BATRA, M., TANDON, P., GUPTA, N., (Postgraduate Clinics), *J. Indian Academy of Clinical Medicine*, **3**(1), 2002, p.23.
26. DEVANAND MANGAR, RICHARD S. LABORDE, DIEN N. VU, *Can J Anaesth*, **40**(3), 1993, p 247.
27. NAMDARI, S., PARK, MIN JUNG, WEISS, A-P C., CARNEY, W.I., *J Hand Surg Am.*, **33**(4), 2008, p.551.

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