

## ORIGINAL ARTICLE

## ACCIDENTAL INTRA ARTERIAL INJECTION AND LIMB ISCHEMIA

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**Background:** Accidental intra-arterial drug injections usually occur as an iatrogenic complication but it is also found in drug abusers as a result of attempted intravenous (IV) injections. It is estimated that accidental intra-arterial injections are found in 1:3500–1:56000 patients visiting emergency department. **Methods:** This was cross sectional study performed in cardiovascular department Lady reading Hospital Peshawar from 1.1.2013 to 31.8.2015. Accidental intra-arterial injection was defined as intravenous injection in upper limb for any illness which is followed by sudden severe pain in limb followed by bluish discoloration of any part of limb. Data was analysed using SPSS-20. Frequency and percentage were calculated for categorical variables like while Means±SD was calculated for numerical variables. *Chi* square test was used to compare Categorical variables. **Results:** Total 30 patients were studied in whom 17 were male. Mean age of the study population was 43.2±17.9 years. All patients after admission were put on intravenous Heparin alone or in combination with Dexamethason, Beraprost and Nifedifin on discretion of visiting consultant. Injection diclofenac were found more frequently as cause of limb ischemia (43 %). Amputation of digits or part of limb was noted in 7 (23.1 %) cases. **Conclusion:** Accidental intra-arterial injection can lead to limb ischemia and even limb loss so while injecting IV drugs, care should be taken to use venous site away from arterial sites.

**Keywords:** Intramuscular; Intraarterial; Heparin; Diclofenac; IV; IM; ABI

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## INTRODUCTION

Accidental intra-arterial drug injections usually occur as an iatrogenic complication but it is also found in drug abusers as a result of attempted intravenous (IV) injections.<sup>1,2</sup> The upper extremity involvement is common and affects mostly the radial and brachial artery due to easier accessibility and proximity to target veins such as the cephalic and basilic vein.<sup>3,4</sup> It is estimated that accidental intra-arterial injections is found in 1:3500–1:56000 patients visiting emergency department.<sup>5,6</sup>

Multiple factors are responsible for limb ischemia due to Intra-arterial (IA) injection, depending on site of injection, type of drug and amount of drug injected. Multiple factors from patient side are responsible for ischemia like vasospasm, thrombosis, acral embolism and thromboembolism. There is lack of clear guidelines for management and multifactorial nature of the problem; it is usually difficult to treat these patients.<sup>3,4</sup> Case reports of intra-arterial (IA) injection have been published since the 1940s,<sup>7,8</sup> Barbiturates and Benzodiazepines are the two commonly reported drugs.<sup>5,9</sup>

Intra-arterial injections can lead to limb ischemia and limb loss.<sup>3</sup> The problem is most severe in IV drug abusers as compared to iatrogenic cases due to their delayed presentation and different type of substances injected, some of which are even not designed for injection.<sup>10,11</sup> They also try some times crushed formulation which enhance complications.<sup>12</sup>

Diagnostic tool involves manual (Allen test) Doppler studies and ankle brachial index. It has found that ABI less than 0.9 have 95% sensitivity and specificity for limb ischemia.<sup>13</sup> Angiography is the gold standard for vascular pathologies including accidental intra-arterial injections. Role of CT angiography, MRI angiography or laser Doppler flowmetry is still not determined.<sup>14</sup>

Treatment depends upon clinical picture and to prevent thromboembolic complications and compartment syndrome.<sup>15</sup> Vasospastic drug effect can be minimized by systemic or local intra-arterial alpha blockade or phosphodiesterase inhibition with drugs like phentolamin and papaverine.<sup>16</sup> Thromboembolic complication can be prevented by intravenous heparin or use of thrombolytic like Recombinant tissue plasminogen activator(rt-PA).<sup>17,18</sup> Surgical embolectomy can be another option in selected cases.<sup>19,20</sup>

This study is important because there is no data worldwide on IA injection induced limb ischemia other than case reports and this study will help to identify the causative drugs, its outcomes and management strategies to save effected limb.

## MATERIAL AND METHODS

This study was conducted in cardiovascular department Lady reading Hospital Peshawar. Data was collected from 1.1.2013 to 31.8.2015 for a period of 32 months. Study design was cross sectional and sampling technique was non-probability consecutive

sampling. All patients who presented to cardiovascular unit either through Outpatient or emergency department for limb ischemia was included in the study. After permission from hospital ethical committee study was initiated. After informed consent, patients whose ischemia was secondary to injection usage were included in the study. Patient whose ischemia was suspected not to be due to injection were excluded from study. Patients with injection ischemia other than upper limb were also excluded from study. Patient with previous history of limb ischemia, peripheral vascular disease, valvular heart disease, and cardiomyopathy were also excluded from study as these conditions can also lead to acute limb ischemia and bias the results. After thorough history about the problem, type of injection and time of presentation, other illnesses, patients were examined to look for all other Conditions which can lead to limb ischemia. ECG, Echocardiography-ray cervical spine and Doppler ultrasound of the effected limb was done in each case. Acute limb ischemia was defined as, sudden and severe pain in limb with bluish discoloration or gangrenous changes in affected limb with or without absent brachial, radial or ulnar pulse, depending on the site of injection and Doppler ultrasound evidence of absent flow in any artery. Accidental intra-arterial injection was defined as intravenous injection in upper limb for any illness which is followed by sudden severe pain in limb followed by bluish discoloration of any part of limb which fits in definition of acute limb ischemia. Data was collected on pre-specified proforma. Data was analysed using SPSS-20. Frequency and percentage were calculated for categorical variables like gender while Means  $\pm$  SD was calculated for numerical variable like age. Chi square test was used to compare Categorical variables. All results were presented in tabulated form.

**RESULTS**

Over 32 months’ period 30 cases of acute limb ischemia secondary to accidental intra-arterial injections were collected. Mean age of the study population was 43.2 $\pm$ 17.9 years (range 14–70 years). Out of total 17 (56.7 %) were male.

All patients were admitted in cardiovascular ward and were put on intravenous Heparin as weight based regimen and dose was adjusted according to activated Prothrombin time (APTT) as 1.5–2 times the control. All patients were put on intravenous antibiotics. Seven patients were put on intravenous dexamethason as 4 mg twice daily, 5 patients were put on oral prostaglandin Beraprost 20 ug twice daily and 4 patients were put on oral nifedifin 20 mg daily along with Heparin on the discretion of visiting

consultant. All patients stayed for 3–4 days in hospital and were observed for recovery or complications. (Table-1)

Out of 30 cases most of the time injection diclofenac was found as the cause of accidental intra-arterial limb ischemia (43%) whereas injection dimenhydrinate, ranitidine, Heroin and diazepam was found as other causes of limb ischemia. (Table-2)

Out of total 30 patients, 7 (23.1%) underwent amputation of some part of limb depending on the site of injection whether brachial, ulnar or radial artery involvement. Two patients were advised amputation of limb below or above elbow, otherwise Amputation of single or two digits were found in other cases. There was no difference of outcomes among various injections leading to limb ischemia (Table-3). There was no difference in either therapy on the in-hospital outcome. Though it seems that Heparin and combination therapy is better than Heparin alone therapy but its non-significant statistically. (Table-4)

**Table-1: Type of therapy used for limb ischemia**

Type of therapy	Number of patients
Heparin	30
Antibiotics	30
Dexametason	7
Beraprost	5
Nifedipin	4

**Table-2: Causes of injection induced limb ischemia**

Causes	Frequency	Percent
Diclofenac	13	43.3
Dimenhydrinate	6	20.0
Ranitidine	6	20.0
Heroin	4	13.3
Diazepam	1	3.3
Total	30	100.0

**Table-3: Outcome of injection induced limb ischemia**

Drugs causing limb ischemia	Amputation	No amputation	Total	p-value
Diclofenac	2	11	13	0.13
Ranitidine	1	5	6	
Dimenhydrinate	1	5	6	
Heroin	3	1	4	
Diazepam	0	1	1	
Total (n=30)	7	23	30	

**Table-4: Outcome of drugs in injection induced limb ischemia**

Drugs used	Amputation of digits	No amputation	Total	p-value
Heparin alone (n=14)	4	10	14	0.39
Dexamethason+Heparin (n= 7)	1	6	7	
Nifedifin+Heparin (n=4)	1	3	4	
Berapros+Heparin (n=5)	1	4	5	

## DISCUSSION

This study was performed in tertiary care hospital of Khyber Pakhtunkhwa Pakistan which is the only Hospital in the province where cardiovascular surgical facilities are available in Government sector. We receive vascular emergencies from all over the province, Tribal areas of Pakistan and Afghanistan.

Accidental intra-arterial injections leading to acute limb ischemia is very rare condition worldwide and only case reports are present in literature. The magnitude of the problem is high in this part of the world due to poor health services system in the country and quackery system (non-qualified practitioners) is dominant all around especially in rural areas. Most of the time patients go to Quacks and they prescribe injections for every problem. Diclofenac, Dimenhydrinate, Ranitidine injections are most common practice which is done by non-qualified and even uneducated health providers.

We studied 30 cases in period of 32 months, and these are all those cases which were referred to us around the province but probably the problem must be more serious and diverse as many cases must not have been refereed due to poor socioeconomic condition and un awareness and probably many people must have lost their limbs.

In literature, many drugs have been claimed for causing limb ischemia when accidentally injected intra arterially. These drugs include diclofenac, ranitidine, dimenhydrinate, benzodiazepines, phenothiazines, Barbiturates, penicillin, phenytoin, heroin and cocaine.<sup>3</sup> Chang *et al.* described the injection of crushed Zolpidem, which was injected intra arterially. Despite aggressive management gangrenous loss of several digits was seen.<sup>20</sup> Kumar *et al.*, reported a case of a 62-year old male who has been given IA diclofenac sodium injection accidentally. The Patient developed excruciating pain at the site of injection and the limb distal to the injection site. Their patient underwent amputation due to loss of sensation and viability of the distal phalanges.<sup>21</sup> Samanta *et al.*, reported two cases of accidental intra-arterial diclofenac injection, leading to limb ischemia.<sup>6</sup> Another case report was presented by Sen S *et al*<sup>3</sup> who described a healthy 20-year-old college student who was referred for revascularization and skin grafting after 25 mg of intravenous (IV) promethazine was unintentionally infused into the radial artery of his left forearm.

There are four other case reports about accidental IA injection. The first published case of accidental intra-arterial administration of promethazine appeared in 1967. They described that pain and ischemia in those IA was caused by arterial spasm, chemical arteritis, thrombosis, and direct

tissue injury leading to gangrene and eventual amputation. Of the four published cases, only one patient did not develop gangrene. In this case, promethazine was not administered intra-arterially, however, extravasation occurred.<sup>22,23</sup>

We studied 30 cases of Accidental intra-arterial injections leading to limb ischemia. Most of the cases reported here were due to Diclofenac injections (23.1%). Other injections reported were Dimenhydrinate, Ranitidine and Diazepam. Four cases include, Heroin injections used by IV drug abusers. Though Heroin induced ischemia must be more common here but most of these drug abusers are left untreated in streets as there is no proper care and management system present for these people in Pakistan and even these people are found dead in streets so they usually not presented to Hospitals.

We used different treatment modalities for these patients as there is no clear guidelines exist worldwide. We used intravenous Heparin in all cases and most of the patient's limbs were saved using this therapy. Gaspar and Hare<sup>11</sup> proposed a regimen of IV heparin injections every 6 hours for the first 24 hours, and found it successful. It was an old study but it created understanding of the pathophysiology and possible management of the problem. Similar treatment strategy in the form of heparin was proposed by Arquilla *et al.*<sup>14</sup>

Furthermore, we used different drugs along with Heparin to see their effect on in hospital outcome. These therapies include oral long acting nifedifin, oral prostaglandin Beraprost and intravenous dexamethason. Samuel *et al*<sup>24</sup> reported substantial improvement (in 4 hours) in a case of IA injection of heroin in which an IV infusion of iloprost ( $2 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) was used in combination with heparin. Andreev *et al*<sup>25</sup> reported a case of similar success-full recovery of function with iloprost ( $2 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) as part of the treatment regimen along with Heparin. As IV prostaglandins are not available here so we tried oral prostaglandin Beraprost along with Heparin and expected favourable outcomes but the strategy was as effective as other regimes.

Many authors have reported the use of corticosteroids as part of therapeutic regimens for the inflammatory reactions involved with IA injections-both with and without success.<sup>26,27</sup> We also used corticosteroids with IV heparin in some cases but it was not more effective than other strategies.

In our study, there was no difference among all therapies regarding in hospital outcomes but apparently, Heparin monotherapy was less favourable as opposed to combination therapy. Lastly there was no difference regarding in hospital outcomes of ischemia among different injections causing limb ischemia.

Due to the fact that the problem is less common and patients presented less often there is limitation of small sample size, which can't be in fact used for future management guidelines. Though it's a fact that this study is largest study presented so far and is the beginning of an attempt to see the outcomes and various management options for the problem

## CONCLUSION

Accidental intra-arterial injection can lead to limb ischemia and even limb loss so while injecting iv drugs care should be taken to use venous site away from arterial sites.

## AUTHORS' CONTRIBUTION

All authors contributed equally.

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