Inadvertent Intra-Arterial Drug Injections in the Upper Extremity: Systematic Review

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Purpose To review the literature pertaining to inadvertent intra-arterial drug injection in the upper extremity, explore the various treatment options and their outcomes, and identify risk factors for limb amputation following intra-arterial injection.

Methods A systematic review of Medline, EMBASE, and Cochrane databases (inception to March 2013) was completed for patients presenting with intra-arterial drug injection of the upper extremity. Details on intervention and outcome were extracted and subjected to pooled analysis with amputation as the primary outcome.

Results A total of 25 articles (209 patients) were included for review. Mean patient age was 31 ± 8 years (male, 71%; female, 29%). Prescription opioids (33%) were the most commonly injected substance, and the brachial artery (39%) was the most common site. The overall weighted mean amputation incidence was 29%. Anticoagulants were the most common treatment used (77%). From pooled analysis, conditions requiring antibiotic use were significantly associated with a higher incidence of amputation; whereas use of steroids was associated with a lower incidence of amputation. Patients presenting 14 hours or more after injection and those injecting crushed pills rather than pure substances had significantly higher incidences of amputation.

Conclusions Intra-arterial drug injection of the upper extremity carries an amputation incidence of nearly 30%. Conditions requiring adjunctive antibiotic use and delay in receiving care were both significantly associated with higher incidences of amputation. No single treatment protocol to date has established superiority. (*J Hand Surg Am. 2015;40(11):2262–2268. Copyright* © 2015 by the American Society for Surgery of the Hand. All rights reserved.)

Type of study/level of evidence Therapeutic IV.

Key words IVDU, hand ischemia, intra-arterial injections, drug abuse.



NADVERTENT INTRA-ARTERIAL DRUG injection (IADI) of the upper extremity is a rare but potentially devastating phenomenon that can lead to tissue loss or necessitate an amputation. In the past, IADIs were most

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0363-5023/15/4011-0022\$36.00/0 http://dx.doi.org/10.1016/j.jhsa.2015.08.002 often the result of iatrogenic complications during anesthesia procedures. ^{1–10} A steady rise in recreational intravenous drug abuse in the last few decades has made drug users the patient population now primarily affected by this problem. ^{10–15} The 2011 World Drug Report estimated 14 million intravenous drug users worldwide, most of whom reside in the United States. ¹⁶

The clinical sequelae from IADI can include skin necrosis, infections, pseudoaneurysm, rhabdomyolysis, compartment syndrome, and distal ischemia resulting in limb loss. This presents a treatment challenge to hand surgeons who have very little guidance and even less consensus from the literature.

Prior attempts at treating this problem have included medical and invasive therapies. ¹⁷ Anticoagulants, ^{18–22}

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arterial vasodilators, ^{19,20,23,24} and antiplatelet agents ^{19,20} have all been tried with varying success. Angiography has been used for diagnosis and treatment with limited success. ²⁵ Regardless of the type of treatment provided, the amputation incidence IADI ranges from 20% to 100%. ²⁶

To gain insight into the diagnosis and management of IADI of upper extremities, we performed a systematic review of the literature.

METHODS

Literature search

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The Medline (PubMed), EMBASE, and Cochrane databases were searched from their inception to March 2013. Search criteria were formulated to identify all reports of IADIs in the upper extremities by using these search terms: intra-arterial injection, upper extremity, intravenous drug use, upper extremity intra-arterial injection, and upper extremity intravenous drug use.

Study selection

Two independent reviewers (C.D. and K.D.H) identified any potentially relevant articles from the list of titles. Studies were included that met the following criteria: primary study written in English, intravenous drug abusers of any age, and patients presenting with IADI to the upper extremity. Any studies reporting iatrogenic arterial drug injections, lower extremity arterial injections, intravenous drug injections, commentaries, reviews, and animal studies were excluded. Citations in the included articles were reviewed to identify any additional articles meeting inclusion requirements.

Data extraction

Once all relevant articles were selected, manuscript review and data extraction were performed to obtain the following information: patient demographic data, presentation characteristics, substance injected, site injected, diagnostic modalities, medical therapies, surgical interventions, and follow-up time. The main outcome assessed was amputation, defined as any surgical or autoamputation at the digital level or proximal.

Statistical analysis

A summary estimate of the overall mean amputation incidence from all studies (excluding single-patient case reports), weighted based on sample size, was calculated with 95% confidence intervals (CIs) and a forest plot was built (Appendix A; available on the *Journal*'s Web site at www.jhandsurg.org). To determine the effect of various treatment modalities on amputation incidence,

data on intervention and amputation outcome were pooled, producing a study cohort from published case series. All studies describing pseudoaneurysm and studies missing information at the individual level were excluded. From this pooled study cohort, a univariate analysis was done to determine association between each treatment modality and amputation incidence. A multivariable regression model was fitted to estimate the independent effect for each treatment modality after adjusting for concurrent treatments. Given the scarcity of data points, only the 2 strongest confounders were adjusted for in each model. These confounders were identified by the change-in-estimates method following Mantel-Haenszel analysis. 27

Using a similar pooled analysis, incidences of amputation were compared between injections of crushed pills and pure substances (ie, heroin, cocaine) and a critical time point (designated as the median delay in presentation). Significance was tested using chi-square test. Statistical significance was defined as P < .05.

RESULTS

Study selection

The initial search identified 1,888 articles, which were screened to determine their eligibility. An additional 20 studies were identified through manual cross-referencing of citation lists. After applying the eligibility criteria, 25 studies containing 209 patients with IADI were included in the review (Fig. 1). The median year of publication was 1991, and publications ranged from years 1972 to 2011. Twenty-two articles dealt with patients with distal ischemia following IADI, 11,17-19,21-26,28-39 2 articles reported on pseudoaneurysm patients, 40,41 and 1 study reported on both. All 25 studies were retrospective case series or reports.

Study and patient characteristics

Detailed characteristics of included studies are listed in Appendix B (available on the *Journal*'s Web site at www.jhandsurg.org). Mean patient age was 31 ± 8 years; 71% of the patients were male, and 29% were female. The median delay in presentation to the hospital from time of injection was 14 hours. The most commonly injected site was the brachial artery (40%), followed by the radial artery (24%). The most commonly injected substances were nonheroin prescription opioids (33%). Most patients presented with severe pain (78%) and/or cyanosis and mottling (46%). Motor impairment on presentation was reported in 37%, a sensory deficit in 34%, and temperature impairment in 26% of patients. Upon presentation to the hospital, 17% of patients already had some extent of gangrene of

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