Case report

Hyperbaric oxygen treatment in a rare complication of intramuscular injection: four cases of Nicolau syndrome

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Abstract

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Intramuscular injections are one of the most common clinical procedures. The objectives of this case series are to analyse the role, timing and efficacy of hyperbaric oxygen treatment (HBOT) in the management of Nicolau syndrome (NS), an extremely rare complication of this common intervention. Clinical, demographic, laboratory and microbiological data extraction were performed through retrospective analysis of the medical records of all patients with NS who were referred for HBOT over a 10-year period with wounds, ischaemia, infection or necrosis at the injection site following drug injection; four patients with NS were included. All injections were made via the intramuscular route; three adult cases followed a non-steroidal anti-inflammatory drug, diclofenac sodium and one in a child followed penicillin injection. The time between diagnosis/injection and HBOT ranged from five to 33 days. NS can develop despite all preventive measures based on injection technique guidelines. HBOT appeared beneficial to healing of NS when administered with other therapeutic approaches. Due to the missing pieces of the puzzle in pathogenesis, NS is rarely completely reversible; keeping the awareness high for undesirable complications stands out as the most effective approach.

Introduction

Although it is not among the ancient symbols of the medical profession, such as the Caduceus or the staff entwined with serpent symbol that is known as the "*Rod of Asclepius*", the syringe is one of the most widely used devices in interventional medicine and everyday practice. At least 16.7 billion injections are estimated to be administered worldwide every year, the vast majority for curative care.[1] Hyperbaric medicine practitioners are unlikely to be involved in the management of complications due to these injections with a rare exception.[2–4] Nicolau syndrome (NS) was described originally as iatrogenic cutaneous necrosis following intramuscular injection of bismuth salts for the treatment of syphilis. This new clinical entity was described first in 1924 as "*embolia cutis medicamentosa*"; and was highlighted as early-stage livedoid dermatitis and subsequent gluteal gangrene a year later.[5,6] The objectives of this case series were to assess the role, timing and apparent efficacy of hyperbaric oxygen treatment (HBOT) in the management of NS, an extremely rare complication of intramuscular injection.

Methods

Approval was obtained from the Clinical Research Ethics Committee of Canakkale Onsekiz Mart University (2021/03, 03.03.2021) for a retrospective analysis of the medical records of all patients with NS who were referred to the Med-Ok Hyperbaric Oxygen Therapy Centre for HBOT between 1 January 2006 and 30 June 2016 with wounds, ischaemia, infection or necrosis at a drug injection site. The clinical data were reviewed for patient demographic characteristics (age, sex and comorbidities), body mass index (BMI), administered pharmacological agent, administration route, period and frequency, microbiologic evaluation, medical treatment received before HBOT (nature, duration), surgical intervention, HBOT received (number and duration of sessions), interval between onset of symptoms and HBOT and final clinical outcome based on laboratory, radiologic and/or clinical evaluations performed by the referring department.

Prior to HBOT, all patients were evaluated for contraindications such as the presence of untreated pneumothorax, radiologically indicated lung bullae or blebs,

pregnancy, severe emphysema and chronic obstructive pulmonary disease (COPD) assessed by pulmonary function tests, uncontrolled seizure disorders and cardiovascular instability. HBOT was administered in a multiplace hyperbaric chamber once or twice daily, five or six times per week, depending on the severity of the clinical findings. The treatment pressure was 253 kPa and each session consisted of three 25-minute oxygen periods with five-minute air-breaks to reduce the risk of oxygen toxicity. The decision when to terminate HBOT was made by the referring department.

Results

Over a 10-year period, four patients (one male, three female – one a child) were referred (Table 1). The injection site was dorsogluteal in two cases, ventrogluteal and vastus lateralis in one case each. All three adult cases occurred following administration of diclofenac sodium. Low back pain secondary to lumbar discopathy-spondylolisthesis and postoperative shoulder pain were the indications for intramuscular diclofenac administration in two and one patients, respectively. Benzathine penicillin was given intramuscularly for an upper respiratory tract infection in the child. None of the adult patients had a history of smoking. Non-insulin dependent diabetes mellitus was among the comorbidities in one patient, while arterial hypertension was present in two. All four patients had surgical interventions prior to HBOT referral; debridement in the three adults and thigh, leg and foot fasciotomies with dual incisions in the child. The time between diagnosis/injection and HBOT ranged from five to 33 days (Table 1).

In microbiological analyses of deep tissue samples taken from the wounds, methicillin-sensitive *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas spp* respectively were detected in the three adult cases, whilst there was no growth from the child's wounds. An appropriate antimicrobial regimen was chosen in all patients based on microbial sensitivity results and the recommendations of infectious disease consultants. Although the tissue samples were culture-negative, the child received empiric broad-spectrum antibiotic treatment.

The patients had been referred for HBOT for the presence of necrotising soft tissue infection with deterioration or delay in wound healing despite proper wound care, or after refusal

Table 1
The clinical characteristics and course of four patients with Nicolau syndrome who received hyperbaric oxygen treatment (HBOT); F – female; M – male

Patient	1	2	3	4
Gender/age (years)	M/66	F/48	F/76	F/3
Body mass index ($kg \cdot m^{-2}$)	26.1	34.6	30.5	16.0
Injection side/site	Right/dorsogluteal	Left/ventrogluteal	Right/dorsogluteal	Left/vastus lateralis
Drug administered	Diclofenac Na	Diclofenac Na	Diclofenac Na	Benzathine penicillin
Number of injections	1	Multiple	1	1
Comorbidities	Diabetes mellitus	Hypertension	Hypertension	No comorbidities
Microbiology	*Staph. aureus methicillin-sensitive*	*Escherichia coli*	*Pseudomonas spp*	No growth
Treatments prior to HBOT	Debridement	Debridement	Debridement	Heparin, pentoxifylline, fasciotomy
Time from injection/ diagnosis to HBOT (days)	7	32	33	5
Number of HBOT	25	40	28	13
Final outcome	Complete wound healing (before planned HBOT sessions completed)	Complete wound healing (before planned HBOT sessions completed)	Complete wound healing (+ graft reconstruction before planned HBOT sessions completed)	Complete wound healing (+ graft reconstruction in fasciotomy areas without limb loss

Figure 1
Images of the injection site in the left gluteal region of a patient with Nicolau syndrome and evolution of the lesion over three months; A) appearance of the 8 x 5 x 2 cm wound prior to HBOT; B) marked granulation tissue formation in fifth week; C) eighth week; D) third month follow-up

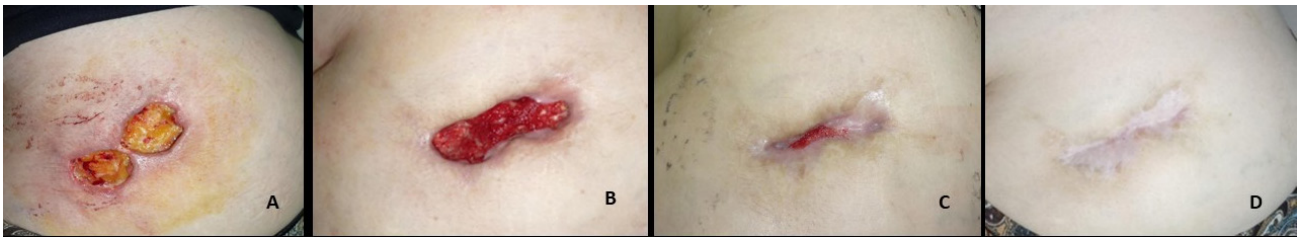
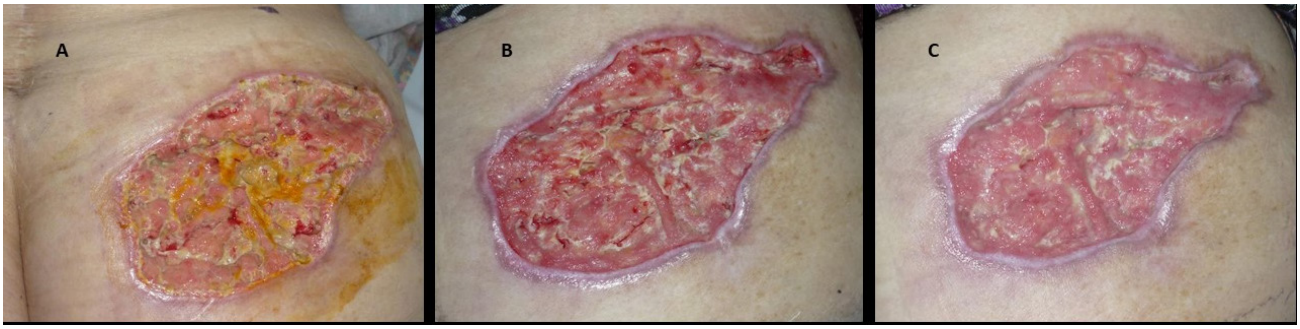


Figure 2
A) Appearance of the injection site of a patient with Nicolau syndrome on presentation to hospital; B) progression of wound (17 x 12 x 1.5 cm) during HBOT at second week; and C) fourth week of treatment; the wound demonstrates good granulation tissue without signs of infection



of further surgical intervention in order to increase oxygen concentration in the affected tissue as an adjuvant to heparin, pentoxifylline and fasciotomy respectively.

The average number of HBOT sessions was 26 (range 5–40), the treatments being well tolerated by all four patients. The three adults received daily wound dressings along with HBOT and all were followed up by the cardiovascular and plastic-aesthetic surgery departments. In two adult patients, complete wound healing without functional impairment was achieved before the planned HBOT sessions were completed (Figure 1), whilst the other two patients underwent skin graft reconstructions (Figure 2). None of the patients experienced limb loss. Post-HBOT physiotherapy rehabilitation was required in one patient who developed compartment syndrome.

Discussion

NS is an adverse dermatological reaction to the injection of a variety of drugs neither limited to bismuth suspensions nor to the intramuscular route.[2–15] Clinically, this rare syndrome is characterised by severe pain at the injection site with the immediate development of pallor and oedema. This is followed by erythematous maculae evolving within hours into livedoid reticular patches and plaques with dendritic extensions which culminate in cutaneous, subcutaneous, sometimes adipose and deep intramuscular necrosis. The necrotising lesion eventually sloughs, and the underlying ulcer evolves towards an atrophic pink scar devoid of adnexa over a few months.[7–14] However, not all cases progress in this predictable manner. NS has also been associated with fatal morbid complications such as widespread cutaneous necrosis, transient or permanent ischaemia of the ipsilateral limb, various neurological disorders, secondary infections, rhabdomyolysis, compartment syndrome and severe renal failure; it may result in medical malpractice claims.[8,9,11,13–15]

Local arterial vasospasm secondary to sympathetic stimulation, arterial embolism caused by the intra-arterial injection of microcrystals and ischaemia caused by compression following vascular or perivascular injection have all been suggested in its pathogenesis. Cytotoxic effects are also highlighted, depending on the composition of the drug, the injection site and individual skin sensitivity.[10–12] Diclofenac sodium may create vasospasm following inhibition of prostaglandin synthesis and cyclooxygenase inhibition.[10,16]

There is no standard treatment regimen. Positive results have been obtained with the use of sympathetic nerve block, heparinisation, arteriotomy and extraction of clot, calcium channel blockers, dipyridamole, trinitrine, pentoxifylline, corticosteroids and HBOT, suggesting that a vascular origin is the most realistic theory.[2–4,8,11] On the other hand, after this acute period and/or the limitation of

necrosis, various treatment regimens have been proposed recently for infection, tissue healing and reconstruction.[17] These algorithms do not include HBOT. In this context, the main inference of this small case series is that HBOT appears to have beneficial effects when combined with other treatments such as antibiotics and appropriate wound care after debridement of necrotic areas that are not progressing satisfactorily.

The rationale for HBOT in the acute phase is based on anti-hypoxic, anti-oedema effects and the mitigation of reperfusion injury. Therefore, it should be initiated as early as possible and administrated more frequently.[2–4] Following a longer interval between the incident injection and referral, HBOT may be of benefit through antibiotic and wound healing-accelerating effects, particularly in complicated cases with secondary infection as in three of the present cases. In the post-acute, early regenerative phase, granulation tissue fills the void caused by the necrosis (Figure 2) after debridement and drainage of abscesses, if any. Resolution of infection and granulation tissue formation may be impeded in the presence of comorbidities such as diabetes mellitus, peripheral vascular disease and obesity.

HBOT helps provide adequate oxygen for fibroblastic activity, leukocyte function, angiogenesis and wound healing in hypoperfused, hypoxic and infected tissues.[18] These benefits are particularly important when primary closure is not appropriate and/or the planned reconstructive surgery is declined by the patient. The long, variable referral interval (up to 33 days in this series) also suggests that hyperbaric physicians may not encounter the early clinical characteristics. Thus, one should be familiar with the course of the syndrome and its unpredictable progression. Moreover, in such presentations, a standard algorithm should not be expected, since therapeutic measures should be based on the clinical status of the individual patient.

Thicker subcutaneous adipose tissue makes it more difficult to reach the target muscular tissue.[19] High BMI, female gender, the use of the dorsogluteal site and diclofenac sodium predominance were consistent with the literature in this series.

Prevention should be the cornerstone of care. Choosing the appropriate needle according to the patient's weight to avoid the risks of subcutaneous injection, preferring different anatomical sites for repeated injections, use of the Z-track method of injection and reassessing the site for any signs of complication after injection are well known and widely practiced measures to avoid this iatrogenic complication.[7,8,10,11,19,20] However, it is unclear whether or not they prevent NS. Particularly in the outpatient setting, where intramuscular administrations are more frequently preferred, healthcare personnel as well as the patient or accompanying adult should be warned about reporting complications without delay and advised how to assess the site.

Conclusions

NS can develop despite adherence to all preventive measures based on injection technique guidelines. As seen in these four patients, HBOT may have beneficial effects in minimising damage when administered with other therapeutic approaches, not only in the acute phase but also later, particularly in cases with compartment syndrome, secondary infection, surgical intervention refusal and/or impaired wound healing. However, due to the missing pieces of the puzzle in the pathogenesis of NS it is rarely completely reversible. It remains unclear how the various approaches to treatment affect the natural course of NS. Maintaining a high awareness for undesirable complications is the most effective approach until the missing pieces are in place.

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