

Nicolau Syndrome after intramuscular injection of non-steroidal anti-inflammatory drugs (NSAID)

Mehmet Dadaci^{1*}, Zeynep Altuntas¹, Bilsev Ince¹, Fatma Bilgen¹, Osman Tufekci², Necdet Poyraz³

¹Department of Plastic, Reconstructive and Aesthetic Surgery, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey, ²Private Farabi Hospital, Physical Medicine and Rehabilitation, Konya, Turkey, ³Department of Radiodiagnostic, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey

ABSTRACT

Nicolau syndrome is a rare complication of intramuscular injection that leads to local ischemic necrosis of the skin and adipose tissue. In this paper, we discuss etiologies, risk factors, and treatment options for gluteal Nicolau syndrome referring to patients treated in our hospital. Our study includes 17 women who visited our clinic with symptoms of gluteal necrosis secondary to intramuscular injection. The following variables were taken into account: injection site, drug administered, frequency of injections, the person who administered the injections, needle size, and needle tip color. Magnetic resonance images obtained in the aftermath of intramuscular injection application were carefully analyzed for presence of necrosis, cyst formation and the thickness of the gluteal fat tissue layer. Drugs that had been received in intramuscular injection were exclusively non-steroidal anti-inflammatory drugs. Mean patient BMI was 41.8 (all patients were considered as obese), and mean gluteal fat thickness was 54 mm. Standard length of needles (3.8 cm) had been used in procedures. The wounds were treated with primary closure in 11 patients and with local flap therapy in 6 patients. The observed necrosis was a consequence of misplaced gluteal injection, where drugs were injected into the adipose tissue instead of the muscle due to the extreme thickness of the fat layer, on one hand, and the inappropriate length of standard needles, on the other hand. Intramuscular injection should be avoided in obese patients whenever possible: if it is necessary, proper injection technique should be used.

KEY WORDS: Nicolau syndrome, intramuscular injections, subcutaneous fat tissue thickness, gluteal necrosis

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INTRODUCTION

Intramuscular injection is used as a technique of choice for application of drugs in many treatment protocols in order to achieve quick and effective response. The best-known and most severe complication of this procedure is a sciatic nerve injury; however, an abscess and/or tissue necrosis may also develop at the injection site [1-5].

Nicolau syndrome (livedoid dermatitis, embolia cutis medicamentosa) is a rare complication of intramuscular injection that usually presents with pain at the injection site, hyperemia, skin discoloration, redness, abscess formation, and local ischemic necrosis involving the skin and adipose tissue. The pathogenesis is not yet clearly understood, but is thought to involve direct vascular damage, perivascular inflammation,

and vascular contraction following injection [1-5]. The properties of the drug injected may play a role; for instance, non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the enzyme cyclooxygenase, preventing thus the synthesis of prostaglandin, consequently inducing vascular spasm, and restricting local circulation [6-10].

The risk of Nicolau syndrome is closely associated with the injection site, the depth of the muscle, the frequency of drug administration, and the action of the drug itself. If the needle tip does not reach the muscle, which often occurs in overweight patients, the administered drug may remain within the adipose tissue. Repeated injections at the same site may also cause complications. Manifestations of Nicolau syndrome range from a sterile or purulent abscess to tissue necrosis [1-6]. The drugs most commonly causing tissue necrosis include phenylbutazone, local anesthetics, antihistamines, anti-inflammatory agents, corticosteroids, and penicillins [4-12]. There have been many case reports on this syndrome; however, only few recommendations have been made regarding the best treatment plan.

*Corresponding author: Mehmet Dadaci, MD, Department of Plastic, Reconstructive and Aesthetic Surgery, Meram Medical Faculty, Necmettin Erbakan University, 42080 Meram, Konya, Turkey, Tel.: +90 332 223 60 00-7965, Fax: +90 332 323 61 81. E-mail: mdadaci@gmail.com

The present study discusses treatment methods that we employed at our hospital for patients with Nicolau syndrome in the gluteal region, as well as possible etiologies and risk factors for the development of this syndrome.

MATERIALS AND METHODS

The study included 17 patients admitted to our hospital between 2010 and 2014 for necrosis at the injection site after intramuscular drug injection employed in treatment schemes for hip or back pain.

Injection site, the type of administered drug, injection frequency, the person administering the injection, needle size, needle tip color, and presence of systemic disease were documented for all patients. Patient weight and height were ascertained, and body mass index (BMI) was calculated. If available, magnetic resonance images (MRIs) were obtained from the hospital's picture archiving and communication system (PACS) and further examined for the presence of necrosis, cyst formation due to injection, as well as for the adipose tissue thickness in the gluteal region. Patients who had previously undergone MRI to determine the cause of their pain and had not experienced significant weight gain or loss (± 5 kg) since their MRI scans were obtained, were also included in the study. For patients who had no MRIs in the PACS, we obtained MRIs in the first year after Nicolau syndrome treatment in order to evaluate gluteal fat thickness and the presence of cysts. The size of the necrotic lesion was measured for all patients.

Debridement was performed at admission to allow preparation of a culture, after which the open wound was dressed daily. Negative-pressure vacuum therapy (V.A.C.

Therapy System, Kinetic Concepts, San Antonio, TX, USA) was administered to treat abscesses and stop leakage from fat necrosis lesions. After leakage was stopped and the cavity was filled, a secondary suture or a local flap was used to cover the wound. Intravenous cefazolin sodium (2×1 g) was administered to all patients. Pathogen-positive patients received an antibiotic chosen on the basis of the antibiogram results.

RESULTS

The clinical characteristics of the patients included in the study are presented in Table 1. Mean patient's age was 61.6 years (range, 41–71 years), and mean duration of hospitalization was 6.6 days (range, 3–12). All patients were female and had a wide hip structure with a gynecoid pelvis. The mean follow-up period was 13 months (range, 6–34 months). Regarding comorbidities, 6 patients had type 2 diabetes mellitus, 8 had hypertension, and 2 had a history of myocardial infarction. All patients had been injected with NSAIDs. Two of the patients had received a single injection, and the others had received more than one. Nine patients had received diclofenac sodium, 5 had received metamizole sodium, and 3 had received dexketoprofen trometamol. The injections had been administered by health-care personnel in 13 patients and by relatives in 4. The necrotic lesion was located in the right gluteal region in 10 patients and in the left gluteal region in 7 patients. The largest necrotic lesion had dimensions of 17×13 cm, and the smallest one 3×4 cm (Figure 1). One patient developed two necrotic lesions, both of them situated in the right gluteal region (Figure 2a). Microbial culture revealed the

TABLE 1. Demographic and clinical characteristics of the patients included in the study

Patient no	Gender/age	Body mass index	Anatomic location (gluteal)	Gluteal region fat thickness (cm)	Wound size (cm)	Dressing	Repair procedure	Inpatient days
1	F/65	52.3	Right	7.1	17×13	VAC therapy	V-Y Advancement flap	12
2	F/55	36.8	Right	5.3	5×6	Standard dressing	Primary repair	5
3	F/68	36.4	Left	4.5	12×8	Standard dressing	Limberg flap	6
4	F/63	45.8	Left	6.3	13×10	VAC therapy	Limberg flap	13
5	F/59	41.2	Right	5.9	15×9	VAC therapy	Limberg flap	10
6	F/71	37.8	Left	4.8	5×3	Standard dressing	Primary repair	4
7	F/52	44	Left	6.2	5×8-3×6	Standard dressing	Primary repair	3
8	F/62	31.2	Right	4.4	5×11	Standard dressing	Primary repair	4
9	F/68	37.4	Left	4.8	9×13	VAC therapy	Primary repair	11
10	F/54	52.1	Right	6.7	10×7	Standard dressing	Limberg flap	3
11	F/57	41	Left	5.4	14×12	VAC therapy	V-Y Advancement flap	12
12	F/69	42.8	Right	5.3	11×4	Standard dressing	Primary repair	3
13	F/41	46.4	Right	5.8	6×4	Standard dressing	Primary repair	3
14	F/65	43.1	Left	4.9	7×8	Standard dressing	Primary repair	5
15	F/73	38.5	Left	4.7	6×11	VAC therapy	Primary repair	10
16	F/65	38.8	Right	4.5	6×12	Standard dressing	Primary repair	6
17	F/61	44.6	Right	5.4	3×4	Standard dressing	Primary repair	3

VAC therapy: Vacuum assisted closure therapy



FIGURE 1. Superficial tissue necrosis in gluteal region



FIGURE 2. Full-thickness tissue necrosis in two areas in gluteal region (A). Image of a patient who underwent primary repair three weeks after the procedure (B)

presence of *Escherichia coli* in the lesions of 2 patients and *Staphylococcus epidermidis* in 6, while no pathogens were found for the remaining 9 patients. The pathogen-positive patients received antibiotics chosen on the basis of the antibiogram results.

The mean BMI was 41.8 (range 31.2–52.3), therefore all patients in the study were considered as obese. The mean gluteal fat thickness, as determined using MRI scans, was 5.4 cm (range 4.4–7.1). Cyst formation was detected on the pre-necrosis MRI scan in 7 patients (Figure 3). Needles of 3.7 cm in length (standard adult size; green or black tips) had been used for the injection of drugs in all patients.

The patients underwent wide debridement of the necrotic areas. After debridement, 6 patients received additional treatment involving negative-pressure vacuum therapy in duration of 6 days. The wounds were closed primarily in 11 patients (Figure 2b) and with a local flap in 6 patients; in the latter, the Limberg flap was used in 4 and the V-Y advancement flap in the other 2 patients. No complications related to the procedures were observed in any of the patients in the early post-operative period.

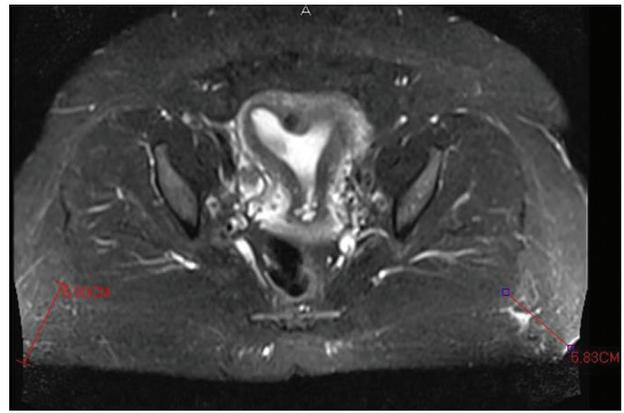


FIGURE 3. Abscess and calcification foci on magnetic resonance cross-sections (subcutaneous adipose tissue thickness: 5.8 cm)

DISCUSSION

The incidence of complications following intramuscular injection varies between 0.4% and 19.3%. Common complications include bleeding at the site of injection, hematoma, accidental intravascular injection, sciatic nerve injury, pain, abscess formation, and tissue necrosis. The post-injection incidence of abscess formation and tissue necrosis is very high compared with the one of sciatic nerve injury [1-6]. In our study, abscesses and calcification foci were visible on MRI scans performed prior to the development of necrosis.

Nicolau syndrome was first described in 1920 as a result of the intramuscular injection of bismuth salt, which was administered for the treatment of syphilis [1-5,13]. Substances reported to cause the syndrome include local anesthetics, antihistamines, the vitamin B complex, NSAIDs (diclofenac sodium, ketoprofen, piroxicam), corticosteroids, diphtheria, tetanus and pertussis vaccines, meperidine and the penicillin group [5-12]. All patients in the present study were considered as obese and had received NSAID injections for relief of joint and low back pain. Fifteen of 17 patients had received multiple injections.

Nisbet [15] measured adipose tissue thickness in gluteal injection sites using pelvic tomography images and found that green needles (length of 3.8 cm) were too short to penetrate beyond the adipose tissue in the anterior gluteal region in 12% of cases. For both regions, the needle was twice as likely not to reach the muscle in female patients as in male patients; in women, the gluteal region is the most important zone of fat accumulation, and women with a higher BMI could be expected to have increased hip fat thickness. In the present study, all patients were female and considered as obese. The mean adipose tissue thickness of the gluteal region contralateral to the affected region was 5.4 cm as determined by MRI, which was 1.6 cm more than length of the 3.8-cm needles used in all patients. As a result, drugs were injected into the adipose tissue instead of the muscle in which they caused severe

toxic effects, impairing circulation, and increasing the risk of fat necrosis. Furthermore, as a result of cumulative effects, a greater inflammation and tissue necrosis were observed in patients who had received repeated injections.

In women considered as obese, the most important fat-accumulating zone is gluteal region. The increased hip fat thickness is usually found in women with a higher body mass index. In the present study, necrosis was exclusively found exclusively in female patients considered as obese that is in concordance with the results reported in literature. Abscesses developing as a complication of misplaced intramuscular drug injection into the adipose tissue could be sterile (i.e., primary) on one hand, and infected, where infection is due to bacterial contamination of the needle tip (i.e. secondary), on the other hand. As a result of fat necrosis, such abscesses may manifest as numerous pockets with multiple, interconnected foci. Therefore, it is crucial to have access into these abscess pockets during abscess drainage and necrosis debridement. Administering negative-pressure vacuum therapy after drainage and debridement ensures the closure of these pockets and contributes to healing by increasing wound granulation and blood flow [15-16].

Most abscesses can be treated using the technique of ultrasound-guided abscess drainage and, if necessary, an antibiotic selected according to antibiogram results could be applied. In the presence of skin and/or fat necrosis, drainage and debridement should be performed without delay. Most tissue defects secondary to the necrosis can be closed primarily; small defects can be left for secondary healing or treated by using negative-pressure vacuum therapy. We experienced no problems in closing small and medium defects due to the flexibility and abundance of the hip tissue; nevertheless, local flaps (V-Y advancement flap, Limberg flap) should be preferred in the case of large defects. There were no postoperative problems in flap circulation and all patients recovered without complications [16].

In obese patients, intramuscular injections should be administered perpendicularly, the needle should be longer than 3.8 cm, and repeated doses should be administered at different sites. The deltoid region is the recommended site; if the injection is to be administered to the gluteal region, the anterior gluteal region should be preferred because of its thinner adipose tissue [4-5, 15-17]. Additionally, it is important to move the needle in order to determine if it is inside the muscle and to administer the injection only when the muscle is not moving. The subcutaneous adipose tissue can be pulled downward beforehand to minimize its thickness (i.e, Z technique).

As obesity rates continue to increase, Nicolau syndrome might appear more frequently. Accordingly, intramuscular injections should be avoided when possible in overweight patients. However, if intramuscular application of drug is

necessary, proper injection technique should be used. In the case of pain, abscess formation and fluid leakage in the aftermath of injection, wide tissue loss can be prevented through early and repeated debridement and proper dressing techniques.

DECLARATION OF INTERESTS

The authors hereby declare that they have no conflicts of interest to disclose.

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