Lesions Associated With Calcium Gluconate Extravasation

Presentation of 5 Clinical Cases and Analysis of Cases Published

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Introduction: Calcium gluconate extravasation is a process, which, while not common, occurs more frequently in neonatal intensive care units. The aim of this study is to present a number of cases of calcium gluconate extravasation, which have occurred in our hospital, and to carry out a review of those clinical cases published in the literature to obtain relevant epidemiological data.

Methods: Data were gathered on the medical histories of 5 patients who presented lesions secondary to calcium gluconate extravasation in our center. A review of the literature was also performed to include clinical cases of calcium gluconate extravasation already published.

Results: Data were collected on 60 cases published in 37 articles. Most patients (55%) were neonates. The average age of these neonates was 8 days. The commonest location of injuries was the back of the hand and wrist (42%). The 2 most frequent symptoms were the appearance of erythema (65%) and swelling/edema (48%) followed by the appearance of skin necrosis (47%), indurated skin (33%), and yellow-white plaques or papules (33%). Most cases are cured within a period of 3 to 6 months. Fifty percent of patients required surgery, and in 13% of cases, skin grafts were performed. The most frequent histological finding was the presence of calcium deposits.

Other histological findings described were the presence of necrosis, lymphohistiocytic infíltrate, and granulomas. Most histological findings were located in the dermis. Most x-rays showing calcium deposits had been performed at 3 to 4 weeks.

Conclusions: Calcium gluconate extravasation is a process, which, although infrequent, is associated with serious skin and soft-tissue lesions, mainly affecting infants. Further studies are needed to determine possible specific procedures to be carried out in these cases.

Key Words: extravasation, calcium gluconate, soft tissue injuries

Intravenous drug administration is associated with a number of complications inherent to the process of injecting a foreign substance into an organism. Extravasation is to be found among such complications. Extravasation is produced when the substance injected leaks out of the vein used for the inoculation, producing the dissemination of the said substance through the soft tissues.

Numerous publications in the literature report the effects caused by drugs when extravasation takes place. In the case of calcium gluconate extravasation, most articles published present isolated clinical cases, and as a result, few publications reflect series that would allow an epidemiological analysis of this process. Calcium gluconate is a salt used to correct a lack of calcium in the blood. It is frequently used with infants, above all in those who require intensive care. Therefore, calcium gluconate extravasation is a process, which, although not commonplace, occurs more frequently in neonatal intensive care units. Given that this process is seldom found, it is hard to perform epidemiological studies in a single center. The aim of this study is to present a number of cases of calcium gluconate extravasation, which occurred in our hospital, and to make a review of the clinical cases published in the literature to obtain the relevant epidemiological data.

MATERIALS AND METHODS

The collection of data on patients who have experienced calcium gluconate extravasation in our center is no easy matter, because, in many cases, no record has been kept of the process (on some occasions, lesions are slight, and no documentary evidence of them is kept in clinical histories). Data were collected from the records of 5 patients who had presented secondary lesions from calcium gluconate extravasation in University Hospital

of A Coruña. The protocols of our center have been followed with regard to the publication of patients' data.

Additionally, a review was made of the literature concerning the subject to include published cases of calcium gluconate extravasation. To review the literature, a bibliographical search was made on Pubmed using the following terms: calcium and extravasation. To select articles for inclusion, the following selection criteria were followed:

Articles that referred to the occurrence of injuries secondary to calcium extravasation in any of their forms;

Articles appearing in the bibliographies of any of the selected articles, which fulfilled the abovementioned premise, were included, even though they did not appear in the results of the original search.

Articles and clinical cases that fulfilled the following criterio were excluded:

Those in which no evidence was provided to show that the cause of the injury was calcium extravasation;

Those in which the route of administration was not intravenous (for example, cases of intramuscular injections of calcium were excluded);

Those in which no information was provided of at least half of the variables under study.

The variables collected were the patient's age and sex, the location of the injuries, the type of calcium used, the dose of calcium, the injuries presented and their evolution, treatment, possible aftereffects, histopathological diagnosis and diagnosis drawn from imaging tests.

Data analysis was performed using the following programs: Microsoft Excel (version 14.5.3) and SPSS (version 21.0).

RESULTS

Cases Registered in our Center

Case 1

One-week-old boy born after 34-week pregnancy presents hypocalcaemia, requiring intravenous treatment with 10% calcium gluconate solution. After experiencing calcium gluconate extravasation in the back of the hand, the patient presents erythema and swelling, with good finger dexterity and color. Topical hydrocortisone was applied, resulting in a partial improvement of the swelling. Two weeks later, the patient was discharged. One week later (that is, 3 weeks after extravasation), an increase in the erythema was noted, with increased local temperature and edema, with mild skin impairment. In addition, some blisters appeared on the back of the hand (Fig. 1). The patient was readmitted to administer intravenous antibiotics. Blisters on the back of the hand were drained, revealing calcium content. Four months after extravasation, the healing process was successfully completed.

Case 2

A 7-month-old boy underwent surgery for hyperinsulinism with associated emetic syndrome. During his stay, he required intravenous treatment with calcium gluconate, presenting extravasation in the dorsum of the left foot. Three days after extravasation, 2 small eschars appeared in the dorsal and lateral regions of the foot, which were treated

conservatively (Fig. 2). The patient was moved to another medical center, and therefore, we were unable to monitor his progress.

Case 3

A 70-year-old woman who experience hyperkalemia within a context of acute kidney failure was admitted to hospital. During her stay, calcium gluconate was administered intravenously. After 24 hours, it was observed that the back of her hand presented edema, erythema, and local heat, so it was suspected that calcium gluconate extravasation had occurred. Burow solution was applied, together with elevation of the affected hand. One week later, the injuries had worsened, and therefore, silver sulfadiazine treatment was initiated. Nine days after extravasation, a necrotic eschar appeared on the back of the hand accompanied by severe pain. One month after extravasation, debridement of the wound was performed, as well as a partial skin graft (Fig. 3A). The graft's evolution was favorable, so the patient was discharged 2 weeks later. Three months on, the curing process had been successfully completed (Fig. 3B).

Case 4

A girl born after a 40-week pregnancy experiences calcium gluconate extravasation on the back of her right wrist after 3 days of life. She presents erythema, local swelling, and a blister-like lesion. Treatment was begun with silver sulfadiazine and antibiotics, administering ceftriaxone and gentamicin intramuscularly. Seven days later, a whitish patch appeared on the back of the wrist in question. One week on, the patient presented a necrotic eschar in the affected area (Fig. 4A). Three weeks after the extravasation, debridement of the necrosis and a partial skin graft were performed. The histopathological

study revealed the presence of ischemic necrosis of the dermis and subcutaneous cellular tissue, along with vascular thrombosis. After 3 months, the curing process was successfully completed (Fig. 4B).

Case 5

A 3-month-old boy born after 31 weeks of pregnancy requires heart surgery for bilateral pulmonary vein stenosis. During his stay in the intensive care unit, experiencing extravasation in the area of the outer right ankle, he required intravenous calcium gluconate treatment. Four days later, the patient presented a necrotic eschar measuring 4 cm x 2 cm (Fig. 5A). Treatment was carried out using silver sulfadiazine. After 2 weeks, debridement of the eschar and partial skin graft were performed (Fig. 5B). One month later, the child died as a result of complications associated with his congenital heart disease.

Review of the Literature

After the inclusion and exclusion criteria, 37 articles were studied, dealing with a total of 60 cases. These articles have been published between 1975 and 2016.[1–37] The ratio of females to males was 1.26:1 (56% women). Patients were classified according to age: 33 neonates (55%) (0–1 month), 8 infants (13%) (2–24 months), 3 preschool-age children (5%) (2–6 years), 4 school-age children (7%) (7–12 years), and 12 adults (20%) (more than 18 years). The average age of neonates was 8 days (median 4). Seventy percent of the neonates were between 0 and 7 days old. The most habitual location of lesions was on the back of the hand and/or the wrist (42%), followed by the upper limb (20%) and the lower limb (18%) (Table 1). The type of calcium involved in extravasation was calcium

gluconate in 70% of cases. The second most frequent was calcium chloride in 17% of cases. The average volumen of calcium infused was 19.2 cc (median 4.9 cc). The 2 most frequent symptoms were the appearance of erythema (65%) and swelling/edema (48%) followed by the appearance of skin necrosis (47%), indurated skin (33%), and yellow-white plaques or papules (33%) (Table 1).

With regard to the treatment provided, half of the patients were treated conservatively by local cures or merely observation. As for applying cold or heat, in 10 cases (17%) local cooling was applied[3,23] and, in just 4 (7%), local heat.[4,10,14,22] Antibiotic ointment was administered in 5 cases (8%)[2,13,14,28] and systemic antibiotic treatment in 9 cases (15%).[3,13,14,19,22,30,32,33] In 2 cases (3%), corticosteroid ointment was administered,[17,28] and in just one (2%), systemic treatment with corticosteroids.[6] Fifty percent of patients required surgery (in 13% of cases, skin grafts were performed)[15,21,25,26,37] (Table 1). One of the series published presented 9 cases in which debridement had been performed using water pressure therapy (Versajet Smith and Nephew Inc, St Laurent, Quebec).[23] In 1 case, intravenous sodium thiosulfate was administered (10 g/dose 3 times weekly for 3 months).[22] Data collected show that surgical treatment was related with the cases with skin necrosis (χ^2; $P < 0.001$) but not with the infected cases (Fisher test; $P = 1$).

A chronogram was designed to assess the injuries' evolution over time, according to the bibliography of works published. We have found that erythema and inflammation appear, above all, during the first 7 days. Nodules and tumors emerge between 7 and 30 days. Papules and whitish or yellowish plaques are produced during the first 4 weeks. Necrosis sets in during the first 3 weeks. These figures are intended as a guide (data collected in the different articles vary). In only 3 cases were signs found of soft tissue infection (2 episodes of cellulite and 1 of purulent discharge).[3,13,35] What does seem clear is that a

complete recovery is made in most cases (63% of cases, among those where the date of recovery is stated) within a period of between 3 and 6 months.

In 11 of the articles (30%), the histopathological study of the injuries is included.[1,3,4,6,8,9,12,22,27,34] The staining used is only reported on in 5 of the articles. In all 5 of these, hematoxylin-eosin was used, whereas in 4, Von Kossa Stain was also employed,[1,4,8,12] and in 2 articles, Alizarin red.[1,27] In 1 article, Giemsa stain was reported to have been used,[4] and an immunohistochemical study was performed in just 1 case.[1] The most common histological finding was the presence of calcium deposits, in 9 articles (82%), most of these being in the dermis. In 2 articles, it is specified that the deposits occurred in the papillary dermis, and in another 2, in the reticular dermis. In just 1 case, calcium was said to have affected blood vessels. Other histological findings included the presence of necrosis (4 articles), infiltration of lymphocytes (3 articles), and granulomas (2 articles). Most histological findings were made in the dermis (7 articles) (Table 2).

In 29 of the cases reported, an imaging study was performed on the affected area.[2–4,7–12,14,16,18–20,22,24,26,27,29–32,35,36] In 27 cases, a plain radiography had been performed; in 1 case, a gallium scan[29]; and in another, a mammography of a skin biopsy.4 In 3 cases, a technetium-99m scintigraphy was performed (in one of these cases, an ultrasound scan was also carried out).

In the 3 cases in which a technetium-99m scintigraphy was performed,[30–32] it was suspected that there might have been osteomyelitis, although this was ruled out afterwards. However, in another of the cases, calcium gluconate extravasation concealed osteomyelitis, which had not been initially diagnosed.[33]

Most x-rays, which presented calcium deposits, had been performed at 3 to 4 weeks, although, in 1 case, the x-ray showed deposits 4 days after the appearance of erythema

and inflammation. Two articles reported that the x-rays performed after 2 and 4 days, respectively, had shown negative results. According to Lee and Gwinn's classification,[38] radiological findings showed a Type 1 calcification pattern in 13 cases, Type 2 in 11 cases, and Type 3 in 2 cases.

DISCUSSION

Calcium gluconate extravasation is a process, which, although infrequent, can cause serious harm, such as the calcification of soft tissues and even skin necrosis. This process is even more serious if we take into account that this complication is more common in neonates, above all during the first week of life. In 1936, Tumpeer and Denenholz[39] published the first account of soft tissue calcification after an intramuscular calcium gluconate injection in a baby's buttock. In that same year, Von Hofe and Jennings[40] published another account of a case of soft tissue calcification after an intramuscular calcium gluconate injection.

The route of calcium gluconate administration was changed from intramuscular to intravenous during the 1940s, but it was not until the 1970s that complications arising from intravenous calcium gluconate began to be reported.[32]

Berger et al[14] in 1974, Yosowitz et al[15] in 1975, and Roberts[10] in 1977 published the first series of cases of soft tissue calcification associated with calcium gluconate extravasation. Goldminz et al[4] published, in 1988, a study reporting an 8% incidence of complications after calcium gluconate injections in premature babies.

According to the literature reviewed, the post-extravasation injuries observed are edema, erythema, and skin hardening. After 7 to 15 days, whitish or yellowish colored plaques

appear, which can lead to skin necrosis.[6] Finally, insoluble calcium phosphate crystal deposits may appear in the affected areas, in the form of hydroxyapatite.[9]

In our bibliographical review, we have seen that the edema and erythema appear at an early stage, during the first 7 days, while plaques and necrosis usually appear during the first 3 weeks. However, in our center, the necrosis appeared precociously, at 3, 4, 7, and 9 days, respectively, in 4 of the 5 cases.

The histological parameters are hard to analyze, given that in only 30% of the articles were biopsies of injuries reported to have been performed. The presence of calcium deposits was only confirmed in 9 cases, which limits the accuracy of diagnosis of calcinosis cutis after extravasation. At any rate, erythema, edema, plaques, and necrosis are signs explored physically, and consequently, we believe that, in the case of calcium gluconate extravasation, histological analysis of injuries is unnecessary for their correct management. Initial post-extravasation x-ray control is of little help as calcium solutions are radiolucent,4 radiographic manifestations appearing at 1 to 3 weeks. Injuries resolve within 2 to 6 months,[2,3] a result similar to that obtained in our review. In 1975, Lee and Gwinn[38] described the 3 patterns observed in an x-ray after calcium gluconate extravasation. In the Type 1 pattern, calcification is observed as an amorphous mass close to the injection site, simulating a myositis ossificans or periostitis if occurring close to a bone. In Type 2, calcification appears diffusely in subcutaneous plaques. This pattern can be taken for fat necrosis, and, in older children, for dermatomyositis. In the Type 3 pattern, vascular and/or perivascular calcification occur. This pattern mimics the signs of arteriosclerosis. If produced on a neonate's scalp, calcifications cause what is known as the “railroad track” sign, similar to those produced in Sturge-Weber disease, although this latter form of calcification is not generally present during the first year of life and is

generally located in the posterior parietooccipital region. Calcifications appear in imaging tests between the first and third weeks of extravasation and disappear around 8 to 12 weeks later. Among the cases reviewed in the bibliography, 50% present a Type 1 pattern, 42% Type 2, and just 8% present a Type 3 pattern.

No clear consensus exists regarding management of the injuries produced by calcium gluconate extravasation. Reviewing published cases, we have seen that half of the patients were managed conservatively, whereas the other half required surgery. Conservative treatment varies and, in most published cases, is unspecified, even though the cases where local cooling is applied as initial management (17%) outnumber those where local heat is applied (7%). The relationship between the symptoms presented and the treatment chosen shows that surgical treatment is related to the presence of skin necrosis. With regard to the use of antidotes in calcium gluconate extravasation, experimental studies have been published about the efficacy of some substances in relation to calcium extravasation, such as the use of hyaluronidase[41] and topical or systemic corticosteroids,[42] although no standardized protocols exist for their use.

CONCLUSIONS

Calcium gluconate extravasation is an infrequent phenomenon, but one associated with serious lesions in the skin and soft tissues, mainly affecting neonates. Even though the injuries produced are usually treated conservatively, the truth is that we lack specific action protocols to prevent the appearance of injuries in these cases, and consequently, the proper approach is to apply antiedema measures (raising the affected limb and cooling locally), local treatments, and, in cases where progress is unsatisfactory, surgery. More studies are needed to determine possible specific action procedures in such cases.

LIMITATIONS

Given that the time period during which the collected articles were published spans about 40 years, data collection lacks uniformity, and some variables were collected in only a few cases (such as the amount of calcium infused, specified in only 14 cases, and the total time to healing, specified in only 11 cases).

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FIGURE 1. Extravasation of calcium gluconate in the back of the hand. The patient presents blister-like injuries with calcium content.

FIGURE 2. Extravasation of calcium gluconate in the dorsum of the foot. Two necrotic eschars can be observed on the outside edge of the foot.

FIGURE 3. A, Extravasation on the back of the hand provoked necrosis, which required debridement. B, Outcome at 3 months of realization of skin graft.

FIGURE 4. A, Skin necrosis caused by extravasation in the back of the hand. B, Three months after the skin graft was made, the healing process was complete

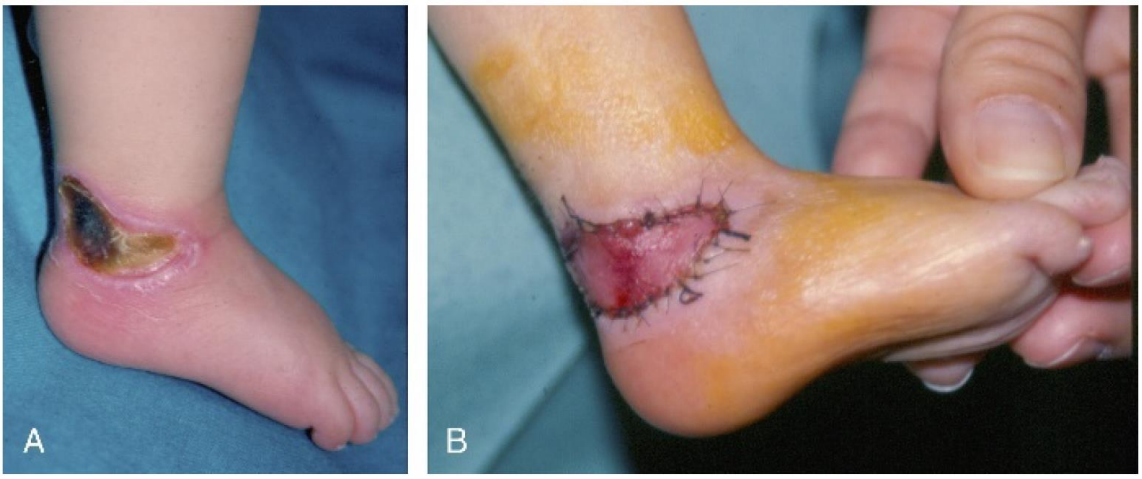

FIGURE 5. A, Necrotic eschar in the lateral malleolus. B, Immediate outcome after partial skin graft.

TABLE 1. Symptoms Presented, Location of Lesions, and Treatments Registered in the Articles Reviewed

	N	%
Symptoms		
Indurated skin	20	33
Nodule/tumor	13	22
Erythema	39	65
Bruising	5	8
Edema/inflammation	29	48
Plaques/papules	20	33
Blisters	12	20
Ulcers	15	25
Eschar/necrosis	28	47
Location		
Scalp	7	12
Upper limb	12	20
Hand/wrist	25	42
Lowers limb/buttocks	11	18
Foot/ankle	8	13
Thorax/back	0	0
Abdomen	0	0
Treatment		
Conservative	30	50
Local cooling	10	17
Local heat	4	7
Topical antibiotics	5	8
Systemic antibiotics	9	15
Topical corticosteroid	2	3
Systemic corticosteroid	1	2
Surgical	30	50
Debridement	21	35
Debridement and grafting	8	13
Fasciotomy	1	2

TABLE 2. Locations and Histopathological Findings in Different Soft Tissue Layers

Layers	Calcium	Necrosis	Granulomas	Neutrophils	Lymphocytes	Eosinophils	Histiocytes	Mastcells
Epidermis	0 (0%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dermis	8 (73%)	1 (9%)	1 (9%)	1 (9%)	2 (18%)	1 (9%)	1 (9%)	0 (0%)
Subcutaneous	0 (0%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (9%)	0 (0%)
Fascia/muscle	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vascular	1 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
N/D	0 (0%)	1 (9%)	1 (9%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)
Total	9 (82%)	4 (36%)	2 (18%)	1 (9%)	3 (27%)	1 (9%)	2 (18%)	0 (0%)

N/D, no data available