SCIENTIFIC LETTERS

False positives in urine methadone screening secondary to tapentadol

Falsos positivos en el despistaje de metadona en orina secundarios a tapentadol

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Tapentadol (Palexia®) is an atypical opioid analgesic, which has been available in Spain since 2011. It is indicated for the treatment of pain that only responds to opioid analgesics, which can be either acute, moderate to intense, or chronic[1]. It acts synergistically as an opioid receptor agonist μ and as a noradrenaline reuptake inhibitor, which explains its analgesic potency[2].

There is an increase in the use and abuse of opioids worldwide, to the point that the U.S. Centers for Disease Control and Prevention (CDC) recommends urine testing for the abuse of non-prescribed substances[3]. The most common methods for these screening tests are immunoassays. Therefore, it is important that the professionals who request them know their limitations. Immunoassays for opiates were designed to identify heroin addiction by detecting its main metabolite, morphine. However, the ability to detect other semi-synthetic opioids (oxycodone, oxymorphone, hydrocodone, hydromorphone, and dihydrocodeine) and synthetic opioids (methadone, buprenorphine, fentanyl, tramadol, and meperidine) is low or non-existent, and false negatives (FNs) may occur. For this reason, more specific immunoassays have been developed, including the immediate metabolite of heroin, 6-monoacetylmorphine. False positives (FP) have also been documented in immunoassays for opiates (quinolones and rifampin[4]) and for synthetic opioids. These include risperidone in fentanyl immunoassay[5] and amisulpride, sulpiride and codeine in buprenorphine immunoassay[6]. Tapentadol has generated FP results in the methadone immunoassay[7]. In addition to tapentadol, FP caused by vortioxetine, diphenhydramine, doxylamine and verapamil have been documented in methadone immunoassays[4,7,8].

The analytical strategy in clinical and forensic toxicology laboratories is to confirm the positive results obtained by immunoassays. This is done using methods based on mass spectrometry (liquid chromatography coupled to tandem mass spectrometry; LC-MS/MS or gas chromatography coupled to mass spectrometry; GC-MS)[4]. Recently, it has also been possible to apply LC-MS/MS directly to detect a large number of substances, avoiding initial screening[9]. Unfortunately, confirmation protocols are not widespread in Spanish emergency departments (ED) due to the lack of technological availability in hospital laboratories.

Patients with chronic pain primarily come to the ED for inability to control pain. They also suffer from greater mental health problems than the general population[10]. Drug screening tests on urine can be requested depending on the history, clinical factors and current ED protocols.

The objectives of the present study were: 1) to analyze the profile of patients with a PF to methadone secondary to tapentadol treated in the ED; and 2) to analyze the degree of concordance between the results obtained by immunoassay with those obtained with the confirmation methods and the patient's medication.

A retrospective observational study was conducted between 2016 and 2019 of patients seen in the EDs of two hospitals in which tapentadol was confirmed after detection of a positive methadone screening test (methadone DRI® immunoassay). Sex, age, reason for consultation, toxic habits, pathological history related to chronic pain, usual medication and diagnosis at discharge were recorded. Drug confirmation and extended toxicology screening was performed by GC-MS (Agilent HP7890A/5975C, Agilent Technologies). Specifically, the diagnostic ions for detection of underivated tapentadol were m/z 58, 59, and 221. Serum ethanol was determined by an enzymatic method (alcohol dehydrogenase).

Tapentadol was detected in 5 (1.25%) patients out of 399 urine drug confirmation tests. No methadone positive was detected for any other substance; in one patient tapentadol was detected in two episodes. Clinical data and toxicological results are presented in Tables 1 and 2. All 5 patients had in common a pharmacological treatment against chronic pain and alcohol or drug addiction problems. All 5 cases presented a PF result for methadone due to the pre-presence of tapentadol.

We found that the detection of tapentadol, the clinical and pharmacological history of the patients, and the fact that none of the other substances detected were associated with methadone FP, would confirm that the common cause of FP was tapentadol. These results are consistent with those found by Collins et al. using the same method[7]. However, they differ from those obtained with the Syva EMIT II® immunoassay in which FP11 was not observed.

Tapentadol undergoes an extensive metabolism, mainly through conjugation (70%), forming glucuronide and tapenade sulfate, and xydation by the CYP450 complex (15%), forming N-desmethyltapentadol and hydroxyltapentadol[2]. Collins et al. postulated that the remaining phenylalkylamine that tapentadol and its metabolites share with methadone is responsible for the cross-reactivity[7].

As for analysis of the degree of concordance between the rest of the results obtained, in case 1, screening and confirmation of benzodiazepines were negative, despite high clinical suspicion; this result could be explained by the presence of a non-inclusive benzodiazepine in the confirmation process, at concentrations below the detection limit or insufficient hydrolysis of glucuronides[12]. A triple FP result occurred in case 2 to amphetamines, ecstasy, and tricyclic antidepressants, caused by trazodone, fenofibrate, and quetiapine, respectively, drugs prescribed by the patient and known to be responsible for FP[4,13,14] results. In case 3, the positive results of cocaine and cannabis were confirmed with the detection of their metabolites. These results are to be expec-

Table 1. Clinical data of tapentadol-positive patients

Parameter	Case 1	Case 2	Case 3	Case 4.1*	Case 4.2*	Case 5
Age (years) / Sex (M/W)	75/M	71/W	44/M		40/M	45/M
Toxic habits	Alcoholism	Severe alcoholism Smoking	Cannabis and cocaine Occasional alcohol	Polydrug addiction in remission Alcoholism		Cocaine Alcoholism
Pathological background (related to chronic pain)	Mixed polyneuropathy Fractures (lumbar vertebra, hip) Functional limitation for moving around	Ulnar neuropathy Osteoporosis	Degenerative osteoarthritis secondary to accident Herniated disks Chronic low back pain Sensitive polyneuropathy	Ankylosing spondylitis		Herniated disks Intense low back pain
Reason for consultation	Decrease in level of awareness (GCS12) Insufficiency acute respiratory	Acute voluntary poisoning (80 tablets 50 mg tapentadol delay) Decrease in level of awareness (GCS 3)	Medication overdose secondary to acute pain (GCS 15)	Visual hallucinations Behavior alteration Clavicular pain	Ethyl alcohol headache poisoning (GCS 15)	Autolytic overeating in the context of alcohol intoxication and chronic low back pain
Tapentadol dosage	25 mg/12 h delay	100 mg/12 h delay	100 mg/12 h delay	250 mg/12 h delay	250 mg/12 h delay	50 mg/12 h delay
Regular medication	Bemiparine, ipratropium bromide, Carboxycillin, dexketoprofen, escitalopram, esomeprazole, spironolactone, fentanyl, furosemide, gabapentin, insulin, lactulose, levofloxacin, lidocaine, sulfate ferrous, tapentadol, vitamins B1, B2, B12	Alprazolam, atorvastatin, calcium carbonate, candesartan, cholecalciferol, escitalopram, Fenofibrate, indacaterol, glycopyronium bromide, omeprazole, paracetamol, pregabalin, quetiapine, tapentadol, trazodone	Cyanocobalamin, metformin, omeprazole, paracetamol, pregabalin, tapentadol, vildagliptina	Buprenorphine, paracetamol, pregabalin, tapentadol, zolpidem (tramadol administered in the ED)	Alprazolam, buprenorphine, lorazepam, lormetazepam, paracetamol, pregabalin, tapentadol	Alprazolam, desvenlafaxine, diazepam, tapentadol, terbutaline, tramadol
Diagnosis at discharge	Hypercapnic respiratory failure with multifactorial respiratory acidosis. Respiratory depression due to benzodiazepine poisoning (false negative inurine)	Intoxication by tapentadol with probable autolithic ideation	Overeating medication with analgesic intent Toxic use disorder (cannabis, cocaine) Probable opiate abuse	Alteration of the sleep pattern	Intoxication by cocaine Social problem	Suicide attempt in the context of adaptive disorder Intoxication by opioids

GSC: Glasgow Coma Scale; M: man; W: woman; ED: emergency department.
*Case 4.1 and 4.2 corresponds to the same patient attended on 2 occasions.

ted, since no FP has been described in cocaine immunoassays, designed against benzoylecgonine, nor in the DRI® immunoassay for cannabinoids used[4]. In case 4, in the first episode the FP to tapentadol and in the second, a FP to amphetamines due to MDMA[14]. Finally, in case 5 the positives for cocaine, buprenorphine and benzodiazepines were also confirmed.

Urine drug screening is particularly useful when patients do not report substances consumed or when they have an altered mental state of unfilial origin[15]. Cases 1 and 2 would be included in the latter case. The definitive diagnosis, however, was only possible after confirmation tests. On the other hand, the drug addiction profile of the other cases made the use of methadone or amphetamines plausible, which was denied by the confirmation tests. Among these cases, Case 4, a polydrug addicted, multi-frequency patient, who had already presented acute methadone intoxication, stands out.

The detection of tapentadol is only possible if a targeted search is conducted, so the actual incidence of this substance may be underestimated. Due to the retrospective nature of the study, its quantification was not possible.

Patients with chronic pain and addiction problems seen in the ED may need to request a urine drug test. These tests complement the diagnosis and guide possible treatments. However, they have limitations, as can be seen in the series of cases presented. The results serve to alert the possibility that in patients being treated or intoxicated with tapentadol, erroneous results may also be generated. All of

Tabla 2. Analytical results of patients positive for tapentadol

Toxicological study	Case 1	Case 2	Case 3	Case 4.1*	Case 4.2*	Case 5
Qualitative test positive for: (immunoassay)	Methadone	Methadone Benzodiazepines Amphetamines Ecstasy ADT	Methadone Cocaine Cannabis	Methadone	Methadone Benzodiazepines Cocaine Amphetamines Ecstasy Buprenorphine Etilglucuronide	Methadone Cocaine Benzodiazepines
Confirmation of methadone and EDDP (GC-MS)	Negative	Negative	Negative	Negative	Negative	Negative
Positive confirmations and detection of other drugs and medicines (GC-MS)	Tapentadol Escitalopram	Tapentadol Alprazolam Trazodona Fenofibrato Quetiapina Escitalopram	Tapentadol Cocaine, Ecgoninamethyl ester, Methylecgonine, and Benzoylecgonine THC-COOH	Tapentadol	Tapentadol Diazepam, Nordiazepam, Oxazepam, Alprazolam, Lormetazepam and Lorazepam Cocaine, Ecgoninamethyl ester, Benzoylecgonine MDMA, MDA Buprenorphine[a] Pregabalina Acetaminophen	Tapentadol Cocaine, Ecgoninamethyl ester, Benzoylecgonine Tramadol Desvenlafaxine Benzodiazepines: not determined[b]
Serum Ethanol	< 0.1 g/L	< 0.1 g/L	< 0.1 g/L	< 0.1 g/L	< 0.1 g/L	0.77 g/L

[a]Confirmation by LC-MS/MS. [b]Insufficient urine sample for confirmation of benzodiazepines.
ADT: tricyclic antidepressants; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (main metabolite of methadone); MDMA: 3,4-methylenedioxy-methamphetamine (ecstasy); MDA: 3,4-methylenedioxyamphetamine (main metabolite of ecstasy); THC-COOH: 11-nor-D9-THC-9-carboxylic acid.

this reinforces the need for the existence of reference toxicology laboratories, as well as the creation of circuits for referring samples between hospitals to these laboratories.

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The COVID-19 curve, health system overload, and mortality

Curva pandémica COVID-19, sobrecarga sanitaria y mortalidad

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The 2019 coronavirus disease pandemic (COVID-19) is an unprecedented stress test for all national health services, starting with primary care and emergency services, and continuing through the rest of the hospital and healthcare structure. The city of Madrid is the most affected in Spain, the most populated area (population: 6,663,394; 47.8 % men, median age 41.8 ± 22.8 years) with 34,188 cases diagnosed as of April 2nd[1].

Here we present a consecutive series of 914 patients discharged, dead or alive, around that date, from two university hospitals in Madrid (approximately 1,400 beds), in charge of an area of 567,308 inhabitants. Cases were included that were confirmed according to World Health Organization criteria, by RT-PCR (reverse transcriptase polymerase chain reaction), and discharged over a period of 4 consecutive weeks (March 6 to April 2), coinciding with the main peak of the pandemic curve in our community[2].

The median age was 67 ± 17.8 years, 58.6% were men and 70% had some cardiovascular risk factor (Table 1). Of these, 255 patients died (27.8%), being older and with more comorbidities than the patients who overcame the disease. However, previous reports on the Chinese[3] and New York[4] experiences have pointed out, at least in the initial publications, lower hospital mortality, 1.4% and 10.2%, respectively (Table 1).

This fact could be explained by some relevant factors. Firstly, the clinical profile is very different. The first cohort mentioned is young with hardly any relevant comorbidities, while the American one is somewhat closer to the Madrid one, presenting almost ten times more mortality than the first one.

Although mortality was present, most of the patients in both series remained hospitalized at the time of publication. The point at which the population is on the pandemic curve and its relationship to the use or depletion of health resources is probably also relevant. In our centers, a decreasing mortality rate was observed when the health system was able to overcome the extraordinarily high demand (first week: 29.4%, second week: 38.3%, third week: 42.3%, and fourth week: 20.5%), after reaching the peak on the local pandemic curve (March 26, Figure 1)[2]. Regardless of the fact that the complex medical and ethical situation caused by potential shortages of beds, ventilators, or inexperienced personnel, aside from the fact that it is possible that those most susceptible or with more aggressive forms of illness could be admitted earlier, a significant change in treatment patterns with increasing use of hydroxychloroquine (12.5%-10.5%-23.6%-64%; p < 0.001) and lopinavir/ritonavir (1.1%-14.3%-25.4%-59.1%, p < 0.001) is noted.

Finally, as an aspect not usually

Table 1. Clinical characteristics, radiographic and laboratory findings together with their respective complications, treatments and clinical results, according to their vital state. Spanish cohort and its comparison with the initial Chinese study[3] and a New York cohort[4]

	Chinese cohort N = 1.099 n (%)	American cohort N = 393 n (%)	Madrid cohort N = 914* n (%)	Madrid cohort*	
				Dead N = 255 n (%)	Alive N = 659 n (%)
Age					
Average (range)-years	47 (35.0-58.0)	62.2 (48.6-73.7)	71 (55.0-80.0)	81 (74.0-87.0)	66.0 (51.0-75.0)
Distribution (total)	/1.011	/393	/913	/255	/658
0-14 years old	9 (0.9)	–	5 (0.5)	0 (0)	5 (0.8)
15-49 years old	557 (55.1)	–	157 (17.2)	6 (2.4)	15 (22.9)
50-64 years old	292 (28.9)	–	178 (19.5)	14 (5.5)	164 (24.9)
≥ 65 years old	153 (15.1)	–	573 (62.7)	235 (92.2)	338 (51.3)
Female	459/1.096 (41.9)	155 (39.4)	378 (41.4)	281 (42.6)	97 (38.6)
Tobacco habit	/1.085	/393	/806		
Never	927 (85.4)	295 (75.1)	596 (65.2)	148 (58.0)	448 (68.0)
Ex-smoker	21 (1.9)	78 (19.9)	162 (17.7)	60(23.5)	102 (15.5)
Current smoker	137 (12.6)	20 (5.1)	48 (5.3)	19 (7.5)	29 (4.4)
Fever on admission	473/1.081 (43.8)	303/393 (77.1)	734/893 (82.2)	199 (79.3)	535 (83.3)
Symptoms on admission					
Cough	745 (67.8)	312/393 (79.4%)	640 (72.2)	166 (68.0)	474 (73.8)
Sore Throat	153 (13.9)	NA	62 (7.6)	6 (2.7)	56 (9.5)
Fatigue	419 (38.1)	NA	352 (42.3)	119 (51.1)	233 (38.9)
Vomiting	55 (5.0)	75/393 (19.1)	64 (7.6)	14 (6.1)	50 (8.2)
Diarrhea	42 (3.8)	93/393 (23.7)	181 (21.6)	37 (15.9)	144 (23.8)
Myalgia or Arthragia	164 (14.9)	107/393 (56.5)	234 (27.3)	38 (16.2)	196 (31.4)
Dyspnea	NA	222/393 (56.5)	480 (54.9)	156 (63.1)	324 (51.6)
Systolic blood pressure < 90 mmHg	NA	6/393 (1.5)	57 (6.3)	26 (10.2)	31 (4.7)

(Continues)

Table 1. Clinical characteristics, radiographic and laboratory findings together with their respective complications, treatments and clinical results, according to their vital state. Spanish cohort and its comparison with the initial Chinese study[3] and a New York cohort[4] *(Continuation)*

	Chinese cohort N = 1.099 n (%)	American cohort N = 393 n (%)	Madrid cohort N = 914* n (%)	Madrid cohort*	
				Dead N = 255 n (%)	Alive N = 659 n (%)
Comorbidities					
COPD	12 (1.1)	20 (5.1)	71 (7.8)	30 (11.8)	41 (6.2)
Asthma	NA	49/393 (12.5)	46 (5.0)	8 (3.1)	38 (5.8)
Diabetes	81 (7.4)	99 (25.2)	190 (21.5)	76 (31.3)	114 (17.8)
Hypertension	165 (15.0)	197 (50.1)	477 (52.5)	193 (76.0)	284 (43.4)
Obesity	NA	136/380 (35.8)	228 (33.5)	70 (34.1)	158 (33.3)
Cerebrovascular disease	15 (1.4)	NA	88 (10.1)	46 (19.2)	42 (6.7)
Coronary Artery Disease	27 (2.5)	54 (13.7)	59 (6.5)	22 (8.6)	37 (5.6)
Cancer	10 (0.9)	23/293 (5.9)	141 (16.3)	58 (24.4)	83 (13.2)
Chronic kidney disease	8 (0.7)	18/393 (4.6) **	58 (6.9)	39 (16.9)	19 (3.1)
Immunodeficiency	2 (0.2)	14/393 (3.6)	61 (7.8)	28 (13.1)	33 (5.8)
Radiological findings					
Abnormalities in chest radiography: number/ total (%)	162/274 (59.1)	328/393 (83.4)	738/819 (90.1)	218 (90.4)	520 (89.9)
Laboratory findings					
Laboratory findings	4.700 (3.500-6.000)	–	6.030 (4.777-8300)	6.600 (4.965-9850)	5.900 (4682-7.815)
Median Leukocytes (range) per mm^3	–	61/393 (15.5)	110/898 (12.3)	27 (10.6)	83 (12.9)
Leukocytes < 4,000 per mm^3	1.000 (700-1.300)	–	1.165 (600-1.400)	700 (500-1.200)	1.247 (700-1.440)
Medium lymphocytes (range) per mm^3	–	351/393 (90.0)	670/851 (78.7)	208 (84.6)	462 (76.4)
Lymphocyte count < 1,500 per mm^3	168.000 (132.000-207.000)	–	205.963 (147.000-244.000)	164.000 (135.500-208.500)	217.323 (154.000-256.750)
Median platelets (range) per mm^3	–	106/393 (16.0)	237/897 (26.4)	89 (35.2)	148 (23.0)
Platelet count < 150,000 per mm^3	13.4 (11.9-14.8)	13.6 (12.4-15.0)	13.6 (13.0-15.0)	13.0 (12.0-14.0)	13.8 (13.0-15.0)
Elevation in:					
C-reactive protein	481/793 (60.7)	97/223 (43.5)	839/893 (94.0)	246 (98.4)	593 (92.2)
Procalcitonin	35/633 (5.5)	56/331 (16.9)	248/724 (34.3)	87 (43.7)	161 (30.7)
Lactate dehydrogenase	277/675 (41.0)	NA	646/820 (78.8)	208 (88.9)	438 (74.7)
Creatinine (> 1.5 mg/dl)	12/752 (1.6)	63/393 (16.0)	116/862 (13.5)	72 (29.5)	44(7.1)
D-dimer	260/560 (46.4)	44/121 (36.4)	526/785 (67.0)	176 (83.4)	350 (61.0)
Troponin	NA	11/246 (4.5)	53/421 (12.6)	27 (19.9)	26 (9.1)
Ferritin	NA	94/142 (66.2)	320 (65.7)	108 (71.5)	212 (63.1)
Complications during admission					
Sepsis	12 (1.1)	NA	145/879 (16.5)	88 (36.1)	57 (9.0)
Acute kidney injury	6 (0.5)	NA	160/882 (18.1)	114 (46.0)	46 (7.3)
Pneumonia-number/total (%)	972/1.067 (91.1)	NA	836/895 (93.4)	238 (96.0)	598 (92.4)
Heart failure	NA	7/393 (1.8)	56/880 (6.4)	36 (14.9)	20 (3.1)
Treatments					
Antibiotics	637 (58.0)	NA	629/872 (72.1)	195 (78.0)	434 (69.8)
Oseltamivir	393 (35.8)	NA	–	–	–
Remdesvir	NA	17/393 (4.3)	–	–	–
Lopinavir/ritonavir	NA	NA	523/884 (59.2)	152 (62.3)	371 (58.0)
Hydroxychloroquine	NA	250/393 (63.6)	752/884 (85.1)	182 (74.0)	570 (89.3)
Systematic Glucocorticoids	204 (18.6)	46/393 (11.7)	158/872 (18.1)	97 (38.8)	61 (9.8)
Mechanical Ventilation					
Intubation	25 (2.3)	130/393 (33.1)	19/870 (2.2)	14 (5.8)	5 (0.8)
Non-invasive	56 (5.1)	–	156/883 (17.7)	64 (26.0)	92 (14.4)
Admission to Intensive Care Unit	55 (5.0)	NA	20 (2.2)	14 (5.5)	6 (0.9)
Hospital stay days [mean (range)]	12.0 (10.0-14.0)	NA	6 (2.0-8.0)	5 (3.0-9.0)	6 (2.0-8.0)
Evolution					
Hospital discharge (alive)	55 (5.0)	260 (66.2)	659 (72.1)	0 (0)	659 (72.1)
Death	15 (1.4)	40 (10.2)	255 (27.9)	255 (27.9)	0 (0)

* Laboratory data relates to presentation in the emergency department or in the first hours of admission.
**Advanced/terminal kidney dysfunction.
NA: not available.

addressed in studies, resource depletion, emergency saturation, or decreased consultation on other diseases could likely further increase population morbidity rates in these catastrophic months of the pandemic.

The mortality rate in Madrid between March 10 and April 1 was 149.4% higher than estimated (181.4% for men, 109.5% for women, 170.7% for > 74 years)[5].

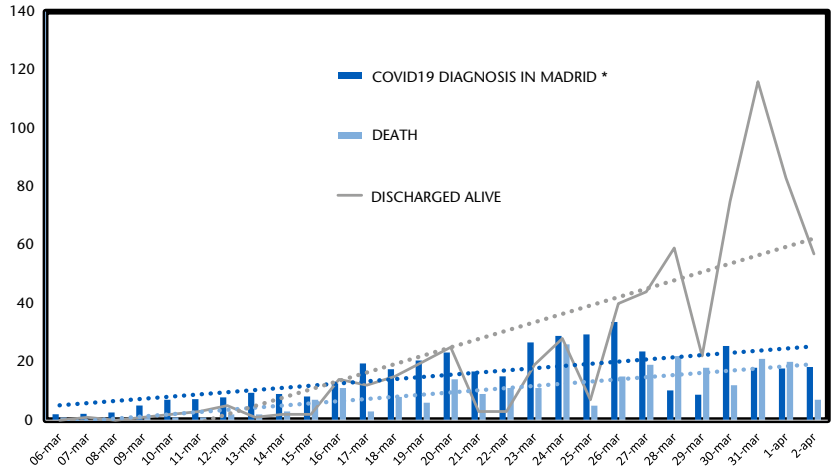

Figure 1. Bar chart showing the newly diagnosed COVID-19 cases in the community of Madrid (dark blue), in connection with our hospital series, deceased (light blue) and discharged patients (grey). The dotted lines correspond to the tendency lines, in their respective colors.
*Multiply by 100 the figure of the numerical scale for patients diagnosed every day in the Community of Madrid.

In conclusion, mortality due to COVID-19 seems to be influenced by many factors. Among them, the explosive and massive presentation of the pandemic outbreak could be relevant in itself, in relation, at least in part, to the overload of health-care resources at the global level.

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Out-of-hospital refractory ventricular fibrillation: characteristics and the use of dual sequential desfibrillation

Características de la fibrilación ventricular refractaria extrahospitalaria y uso de la doble desfibrilación secuencial

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In cardiorespiratory arrest (CRA), ventricular fibrillation (VF) is the heart rhythm with the longest survival. According to the OSHCAR registry, 22.6% of out-of-hospital CRAs have a defibrillable rhythm and a return of spontaneous circulation (ROSC) of 50.6%[1]. Refractory ventricular fibrillation (RVF) includes episodes of VF requiring multiple defibrillations, although there is no consensus on the exact number[2]. This subgroup has a very poor survival rate associated with poor neurological prognosis[3]. In these cases, the European Resuscitation Council proposes progressively increasing defibrillation energy and checking patch placement[4]. It has been suggested that the use of double sequential defibrillation (DSD) could improve the prognosis of these patients[5]. DSD consists of administering two successive electrical shocks, with 2 defibrillators and 4 patches on the chest. The aim of this study is to describe the characteristics of out-of-hospital VFR in our environment, analyze its survival and the possible usefulness of DSD.

We conducted an observational retrospective study of CRA in patients over 13 years old, treated by 061 emergency teams in Andalusia, who required more than 5 defibrillations. The inclusion period was from January 1, 2017 to October 31, 2018. The study was approved by the Clinical Research Ethics Committee in Malaga.

The emergency team had a manual two-phase defibrillator with a shock power of up to 200 J (Corpuls 3 V2.3) and defibrillator patches (Corpatch easy preconnected adult). All patients were treated according to current clinical guidelines. DSD was performed according to the criteria of the medical team and the availability of the resource. Demographic variables were collected (age, sex), clinical variables (initial rhythm, witnessed CRA, recurrent or incessant VF), management variables (previous semiautomatic

defibrillator, previous CRA by control), temporary variables (day or night assistance, response of the first resource, resuscitation time, time to defibrillation) and outcome variables (recovery of CRA and survival at hospital discharge). Survival to hospital discharge and CRA were analyzed according to the type of defibrillation.

In the descriptive analysis the qualitative variables were expressed as absolute frequency, and percentage; the quantitative ones as mean, standard deviation, minimum and maximum. The comparison between groups of the qualitative variables was done with Fisher's exact test, and in the quantitative variables with Student's t-test or with U-Mann Whitney's test if the variable did not follow a normal distribution. It was accepted that there was statistical significance if the p value was < 0.05.

A total of 1,894 CRAs were treated during the study period, of which 486 (25.7%) had a defibrillable rhythm and 40 patients (2.1%) met the criteria for RVF. Table 1 shows the characteristics of the RVFs treated. The age was 59 years (15-84), 28 (73.7%) were male (73.7%), in 28 cases (70%) the assistance took place during the day and in 21 (52.5%) there was CRA performed by control. The initial rhythm was VF in 30 cases (75%) and they received an average of 10 defibrillations (minimum 6 maximum 22).

Regarding the prognosis of patients with RVF, RCE was obtained in 20 patients (50%) and 6 (15.8%) were discharged from hospital alive. The factors related to CPR were response time to the first resource less than 10 minutes (p = 0.02), time to first defibrillation (p = 0.012), time to resuscitation (p = 0.034), and previous CPR performed by control (p = 0.03). Being alive at hospital discharge was associated with a time of less than 10 minutes until care by the first resource (p = 0.01). Table 2 summarizes the characteristics of all the cases that received DSD. DSD was performed in 6 patients (15%), 4 of them presented CRS and 2 were discharged from hospital alive and without neurological sequelae. There was no statistically significant difference between the group that underwent conventional CPR and the group that received DSD.

It is our knowledge that this is the first work that describes the effect of DSD in our environment. The patients included present characteristics similar to those of previous studies[1], although the management highlights a greater performance of CPR per control, this result suggests better training and awareness of the general population. It should be noted that in our study, survival in RVF was similar to that of non-refractory VF; in other previous records, lower survival had been observed[6]. It is noteworthy that of the 6 cases in which this technique was used, in 4 cases CRS was achieved and 2 patients were discharged from the hospital without sequelae. Since this is a very small sample, the differences observed did not reach statistical significance. Cortez et al. obtained 25% of CRS and 17% of hospital discharges without sequelae[7] with a similar DSD technique. Another study that included 45 cases presented a CRS of 38% and a survival at discharge of 7%. In this case, double 360 J shocks and anteroposterior patches were used[8]. More recent studies give RVF cessation figures of 39%, even with 720 J of discharge[9], or 21.4% with DSD in the third shock[10]. There is no evidence of increased survival in RVF CRP with the use of DDS. A recent study

Table 1. Characteristics and survival in refractory ventricular fibrillation

Variables	Total cases N = 40 n (%)	Simple DF N = 34 n (%)	DSD N = 6 n (%)	p
Age. years [min.-max.]	[15-84]			0.73
Mean (SD) (n = 39)	59 (15)	60	57	
Sex (n = 389)				0.64
Woman	10 (26.3)	24 (63)	4 (11)	
Man	28 (73.7)	8 (21)	2 (5)	
Time of the shift				0.65
Day	28 (70)	23 (57)	5 (12)	
Night	12 (30)	11 (28)	1 (2)	
Witnessed CRA				1
No	22 (55)	19 (48)	3 (8)	
Yes	18 (45)	15 (38)	3 (8)	
BLS by witnesses				1
No	19 (47.5)	16 (40)	3 (8)	
Yes	21 (52.5)	18 (45)	3 (8)	
Use of SAD				0.28
No	38 (95)	33 (82)	5 (2)	
Yes	2 (5)	1 (2)	1 (2)	
Initial rhythm				1
VF	30 (75)	25 (62)	5 (12)	
Asystole/PEA	10 (25)	9 (22)	1 (2)	
Recurrent VF				0.38
No	22 (55)	20 (50)	2 (5)	
Yes	18 (45)	14 (35)	4 (10)	
First resource response time (n = 39)	[0-64.5]	13.9 (4.6)	6.8 (7.4)	0.119
[min.-max.]	12.8 (12.5)			
Response time 1st resource				0.41
< 10 minutes	19 (48.7)	15 (38)	4 (10)	
> 10 minutes	20 (51.3)	18 (48)	2 (5)	
Time to first DF (n = 39)	[0-20]			0.482
[min.-max.] [(mean (SD)]	7.9 (6.2)	8.3 (2.3)	5.8 (4.5)	
Time to the first DF				0.67
< 10 minutes	21 (55.3)	17 (45)	4 (11)	
> 10 minutes	17 (44.7)	15 (39)	2 (5)	
Total CPR time in minutes (n = 36)	[16.21-101]			0.841
[min.-max.] [(mean (SD)]	46.9 (20.30)	46.6	48.5	
ROSC (n = 40)				0.66
No	20 (50)	18 (45)	2 (5)	
Yes	20 (50)	16 (40)	4 (10)	
CPR in progress	0 (0)	0 (0)	0 (0)	
Alive at hospital discharge (n = 38)				0.23
No	32 (84.2)	28 (74)	4 (11)	
Yes (CPC 1-2)	6 (15.8)	4 (11)	2 (5)	

RVF: refractory ventricular fibrillation; CPR: cardiopulmonary resuscitation; DDS: double sequential defibrillation; DF: defibrillation; SD: standard deviation; CRA: cardiorespiratory arrest; BLS: basic life support; SAD: semiautomatic defibrillator; PEA: pulseless electrical activity; VF: ventricular fibrillation; ROSC: recovery of spontaneous circulation; CPC: cerebral performance category.

Table 2. Clinical characteristics, management and evolution of cases of double sequential defibrillation

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age	54	47	81	69	48	48
Sex	Woman	Man	Woman	Man	Man	Man
BLS by witnesses	Yes	No	No	No	No	Yes
Response time	5 min	15 min	0 min	16 min	0 min	5 min
Use of SAED	Yes	No	No	No	No	No
Initial rhythm	FV	Asystole	VF	VF	PEA	VF
Recurrent VF	No	Yes	No	Yes	Yes	Yes
No. of single DF	7	15	6	3	14	4
No. of DSD	1	3	1	3	7	2
Time to 1st DSD	35 min	60 min	20 min	23 min	-	10 min
CPR Time	61 min	70 min	23 min	63 min	50 min	36 min
ROSC	Yes	No	Yes	No	Yes	Yes
Hemodynamics	Yes	No	Yes	No	Yes	No
Discharge without sequelae	Yes	No	No	No	Yes	No

DSD: double sequential defibrillation; BLS: basic life support; SAED: semi-automatic external defibrillator; VF: ventricular fibrillation; DF: defibrillation; CPR: cardiopulmonary resuscitation ; ROSC: recovery of spontaneous circulation.

involving 310 patients and in which 71 patients received DSD, DSD was associated with lower probabilities of RECs in pre-hospital cardiac arrest[9]. There are multiple factors that must be taken into account when interpreting studies on RVF and DSD. First, there is great heterogeneity in methodology[11], the definition of RVF itself has not been clearly established[12] and it is recommended to distinguish RVF from recurrent VF[13]. The placement of secondary patches can be either anterolateral or anteroposterior[9]; the anterolateral patch provides more energy, but it can damage the defibrillator[14]. The most effective amount of energy has never been well defined. In our study, 200 J of biphasic defibrillator were used, resulting in 400 J; however, other authors use 360 J in biphasic, at 7 2 0 J[9]. To specify the technique in a differentiated way as sequential or simulated[15] is a priority for the execution of it. Since it is performed manually with one or two operators, there is a lot of variability in time between defibrillations, which influences the demonstration of effectiveness[14].

Considering that the nature of the present study is retrospective and in our service there is no protocol, the difference in management between professionals could be a source of bias. Our survival in RVF is similar to that achieved in other defibrillable rhythms. The use of DSD was not shown to improve prognosis. It is necessary to agree on the definition of VFR, as well as the most appropriate way to perform the DSD technique.

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Spontaneous mediastinal emphysema in patients with COVID-19

Neumomediastino espontáneo en pacientes con COVID-19

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The infection by the new coronavirus SARS-CoV-2 (COVID-19) is challenging internationally in many ways. One of these aspects lies in the clinical suspicion and microbiological diagnosis of our patients. A multitude of possible clinical manifestations have been described (respiratory, digestive, central nervous system, dermal, etc.) that the ED physician should be aware of since they can occur at different stages of the disease.

In patients admitted by COVID-19 and after a satisfactory evolution or in discharges for this disease, a clinical worsening has been evidenced by different clinical situations. We present 3 clinical cases diagnosed with COVID-19, confirmed by reverse transcriptase polymerase chain reaction test (RT-PCR) of nasopharyngeal aspiration, which were attended in an emergency department, as well as in hospitalization rooms, and whose cause of clinical worsening was due to the appearance of a pneumomediastinum.

The presence of gas in the mediastinum is a rare complication that can be secondary to anaerobic infections, tracheoesophageal trauma, or secondary to mechanical ventilation, both invasive and non-invasive. When the previous causes are ruled out, it is called spontaneous pneumomediastinum (SPM) and is produced by an overdistension of the alveoli that leads to their rupture and the passage of air into the interstitium. In the SPM, the air dissects the peribronchial and perivascular planes to reach the mediastinum and then to reach the neck, the retroperitoneum and the subcutaneous cellular tissue. It can be associated with pneumothorax, subcutaneous emphysema, pneumoperitoneum or pneumopericardium[2]. The cardinal symptom is retro sternal chest pain that radiates to the neck and arm, associated with dyspnea, tachypnea, dysphagia and cough. Some patients present to auscultation dry crackles in cardiac focuses coinciding with the heartbeat, due to the presence of air in the pericardial sac; this is known as the Hamman's sign[3-5].

Case 1. A 66-year-old man with no personal history of interest, who was admitted to the hospital for a 5-day period of 37.2ºC fever with mucopurulent expectoration and asthenia and bilateral patchy involvement in the chest X-ray. During his admission, a dimer 2,263 ng/ml (0-500 ng/ml), 500 lymphocytes/µL, ferritin 1300 ng/ml (30-400 ng/mL) and interleucia-na-6 (IL-6) 610 pg/ml (0-7 pg/ml) stood out in the analysis performed. On the 18th day since the beginning of the clinic -13th day of admission-, he presented worsening of arterial oxygen saturation by pulse oximetry (95% to 90% with oxygen with mask at 12 bpm), without increase of dyspnea. In view of the clinical and analytical data, it was decided to start treatment with intravenous methylprednisolone 500 mg (iv) and tocilizumab 600 mg iv., both in single dose, and she was transferred to the intensive care unit (ICU) due to the need for high flow therapy with nasal cannula (HFNC). Three days after his admission to the ICU, a chest computed tomography (CT) scan was requested where pneumomediastinum was targeted (Figure 1A), which was treated symptomatically. In retrospect, visualizing the chest X-ray, on the 17th day of the clinic it was already possible to objectify subcutaneous emphysema in the cervical region (Figure 1A).

Case 2. A 69-year-old male; with a background of myocardial infarction, arterial hypertension, diabetes mellitus type 2, bronchial asthma, rheumatoid arthritis in chronic treatment with corticoids and leflunomide, and ex-smoker. He had been admitted for 10 days for COVID-19, with bilateral interstitial affectation in the thorax radiography and he received treatment with conventional oxygen therapy. He was admitted to the ED on the third day after discharge with stress dyspnea clinic with arterial oxygen saturation at 70% with FiO_2 0.21 and with a reservoir mask at 15 bpm, O_2 saturations of 88% were achieved. D-dimer 49,989 ng/ml, 2,350 lymphocytes/µL, ferriti-na 279 ng/ml and IL-6 15 pg/ml. Urgent CT scan was requested to rule out pulmonary thromboembolism, and pneumomediastinum, pneumopericardium (Figure 1B) and bilateral pneumothorax were observed.

Case 3. An 87-year-old male with a background of colon neoplasia in complete remission. He came in after 6 days of distermal sensation, non-productive cough and increase of dyspnea until minimal-moderate efforts, with bilateral peripheral infiltrates in the chest radiography. After 12 days of hospitalization, he presented resting dyspnea, with a drop in arterial oxygen saturation from 93% to 69% with 15 L in a reservoir mask, so he was assisted with Boussignac type CPAP. On exploration, there was crepitation at digitopressure in the upper left hemi thorax area. A chest CT scan was performed, which revealed a pneumomediastinum and a mild left pneumothorax could be visualized (Figure 1C). On admission, D-dimer 41,316 ng/ml, lymphocytes/uL 456, ferritin 635 ng/ml and IL-6 58 pg/ml were observed.

The three patients had received as treatment: hydroxychloroquine (400 mg/12 h on the first day and 200 mg/12 h until completing 7 days) and azithromycin (500 mg on the first day and 250 mg/day until completing 7 days) since admission. Patients 1 and 3, as previously described, received corticosteroids iv.

Pneumomediastinum can be associated with the joint presence of pneumothorax and pneumopericardium. None of the patients had been exposed to the use of mechanical ventilation -although one of them received oxygen therapy with CPAP prior to the diagnosis-, nor did they present chest pain or any Hamman's sign; in them the main alarm sign was the worsening of arterial oxygen saturation. Although the physiopathological mechanism is unknown; in the context of COVID-19, diffuse alveolar damage[6] occurs, probably secondary to the hyperinflation syndrome these patients suffer. There are no data on the mechanism of this damage, but it is possible that the alveoli are prone to rupture caused by a sudden increase in intralveolar pressure, such as coughing or vomiting, which caused alveolar rupture and air leakage with interstitial emphysema[8]; this could be the cause of the appearance of this entity.

In conclusion, the appearance of pneumomediastinum[9] may be found, together with pneumothorax, super-infection or pulmonary thromboembolism, as causes of clinical worsening in patients with COVID-19.

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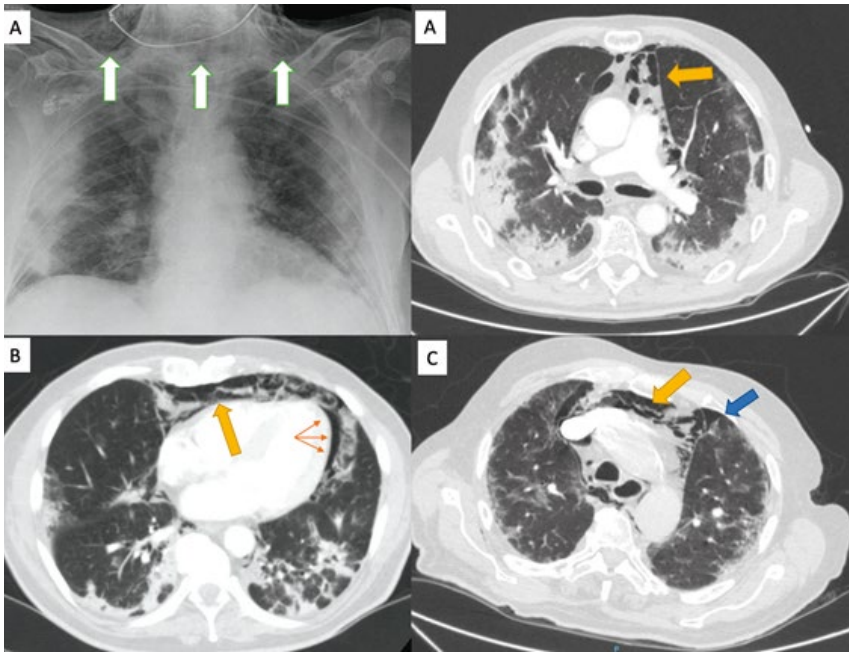

Figure 1. Chest CT scans of the patients presented where the alterations described in the text are observed. White arrows: subcutaneous emphysema; yellow arrows: pneumomediastinum; red arrows: pneumopericardium; blue arrow: pneumothorax

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