



## Opioid-related compartment syndrome and associated morbidity

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### ABSTRACT

**Introduction:** Opioid-related compartment syndrome (ORCS) is an understudied complication related to opioid overdose. We hypothesized that ORCS would be associated with worse clinical outcomes, including higher amputation rates, need for multiple surgical procedures, and rhabdomyolysis on admission, compared with nonopioid-related compartment syndrome (NORCS).

**Methods:** We used *Current Procedural Terminology* codes for fasciotomy as a proxy marker for cases of compartment syndrome treated at 1 health system from January 1, 2016, to December 21, 2018. We excluded patients younger than 18 years, those treated for exertional compartment syndrome, and those who underwent elective fasciotomies. Seventy-four patients met our inclusion criteria. Data reviewed included patient characteristics, cause of compartment syndrome, time until evaluation for compartment syndrome, peak creatinine kinase levels, number of surgical procedures required, duration of hospital stay, and postoperative inpatient morbidity and death. Patients were categorized as having ORCS (n = 8) or NORCS (n = 66). Alpha = .05.

**Results:** All cases of ORCS occurred in men. Opioid use was the third most common cause of compartment syndrome. Two patients underwent amputation, both in the ORCS group ( $p < 0.01$ ). The median number of debridements was significantly higher for the ORCS group (median, 4; interquartile range [IQR]: 3–6) than for the NORCS group (median, 3; IQR 2–4) ( $p = 0.03$ ). Duration of hospital stay was longer for the ORCS group (median, 27 days; IQR 16–38) compared with the NORCS group (median, 9 days; IQR: 5–13) ( $p < 0.001$ ). Mean ( $\pm$  standard deviation) peak creatinine kinase level was significantly higher in the ORCS group ( $224,000 \pm 225,052$  U/L) compared with the NORCS group ( $7550 \pm 32,500$ ) ( $p < 0.001$ ). The proportion of patients who underwent hemodialysis was higher in the ORCS group (88%) than in the NORCS group (35%) ( $p < 0.001$ ). All ORCS patients presented  $>8$  h after immobilization in a dependent position.

**Conclusion:** Patients in the ORCS group had delayed presentations and significantly more morbidity compared with patients in the NORCS group.

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### Introduction

The incidence of opioid use and misuse has increased dramatically in the United States during the past decade, with an estimated 2 million Americans meeting the criteria for opioid use disorder [1]. In 2015, more than 140,000 emergency department visits occurred because of opioid-related poisonings (44 per 100,000 people) [2]. In 2017, opioid overdose deaths increased by 12% from the previous year, totaling more than 47,000 (15 per 100,000 people) [3]. Several complications are related to opioid overdose, including respiratory and cardiac depression and

depressed mental status. Compartment syndrome secondary to opioid use, or opioid-related compartment syndrome (ORCS), is an uncommon and understudied orthopaedic complication of opioid abuse. Acute compartment syndrome occurs after a focal insult to a limb and is characterized by increased intracompartmental pressure resulting in tissue ischemia and subsequent injury to muscles, nerves, and blood vessels [4]. It is suspected that prolonged unresponsiveness and extended periods of immobility, during which tissues are subject to external pressure, can lead to ORCS [5].

Research is limited regarding ORCS. In a series of 22 patients with heroin-related compartment syndrome, Bennis et al. [5] reported that all patients presented with rhabdomyolysis, and more than half presented with acute kidney injury. Ultimately, 1 patient underwent an amputation. Apart from this series, the literature on ORCS is limited to case reports [6–24].

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To our knowledge, no comparative studies have analyzed clinical outcomes of patients with ORCS versus nonopioid-related compartment syndrome (NORCS). Given the increase in opioid misuse across the country and an anecdotal increase in the number of ORCS cases treated at our institution, we sought to analyze and compare the clinical outcomes of ORCS and NORCS. We hypothesized that ORCS would be associated with worse clinical outcomes, including higher amputation rates, need for multiple surgical procedures, and rhabdomyolysis on admission, compared with NORCS.

## Methods

Our study was reviewed and approved by our institutional review board.

### Patients

Patient data were obtained from our multicenter billing database and represented patients treated at 4 centers in our institution. We used *Current Procedural Terminology* codes (Appendix) for upper- and lower-extremity fasciotomy as a proxy marker for cases of compartment syndrome to avoid misclassification that could arise by using *International Classification of Diseases* codes in patients receiving complex trauma care.

We identified 149 patients treated operatively for acute compartment syndrome from January 1, 2016, to December 21, 2018. After excluding patients younger than 18 years ( $n = 17$ ), those treated for exertional compartment syndrome ( $n = 26$ ), and those who had elective (non-urgent) fasciotomies as part of planned procedures ( $n = 32$ ), 74 patients were included in our study. The ORCS group consisted of 8 patients (all men). The NORCS group consisted of 66 patients (18 women). The groups were similar in terms of mean ( $\pm$  standard deviation) age ( $38 \pm 11$  vs  $43 \pm 16$  years, respectively;  $p = 0.42$ ) and body mass index ( $28 \pm 4.9$  vs  $28 \pm 6.3$ , respectively;  $p = 0.87$ ) (Table 1).

### Data review and outcome measures

Two authors reviewed the medical records of all 74 patients. We extracted data on patient characteristics, causes of compartment syndrome, peak creatinine kinase levels, number of patients who underwent urgent hemodialysis, number of surgical procedures, and postoperative inpatient morbidity and death. Additionally, we evaluated the number of adjacent compartments released (1 or  $>1$ ). Each aspect of the extremity requiring fasciotomy was

documented (e.g., leg versus thigh versus gluteal compartments) as a single-compartment release.

### Statistical analysis

Statistical analysis was performed using 2-sample t-tests for numeric data and Fischer exact tests for proportions using Stata, version 12.0, software (StataCorp LLC, College Station, TX). Significance was set at  $p < 0.05$ .

## Results

The most common cause of compartment syndrome was trauma, with 44 cases related to acute injuries (Table 2). The next most common cause was vascular insult ( $n = 12$ ). Compartment syndrome could be directly linked to the abuse of opioids in 8 patients (Table 3), which made opioids the third most common cause. All ORCS patients had delayed presentation after immobilization in a dependent position for at least 8 h. There were no delayed presentations among NORCS patients.

Patients in the ORCS group had a significantly higher mean peak creatinine kinase level ( $224,000 \pm 225,000$  U/L) compared with patients in the NORCS group ( $7550 \pm 32,500$  U/L) ( $p < 0.001$ ). The proportion of patients who underwent urgent hemodialysis was greater in the ORCS group ( $n = 7$ ; 88%) compared with the NORCS group ( $n = 2$ ; 3.0%) ( $p < 0.001$ ), with 2 patients in each group requiring long-term dialysis after hospital discharge.

The number of surgical procedures, including debridements, was significantly higher in the ORCS group (median, 4; interquartile range [IQR]: 3–6) than in the NORCS group (median, 3; IQR: 2–4) ( $p = 0.03$ ). Fifteen patients (7 [88%] in the ORCS group and 8 [12%] in the NORCS group) had  $>1$  set of compartments released ( $p < 0.001$ ). Two patients underwent amputations (transfemoral); both were in the ORCS group ( $p = 0.01$ ). Hospital stays were significantly longer for the ORCS group (median, 27

**Table 2**

Causes of compartment syndrome in 74 patients treated at 4 sites of 1 health system, 2016–2018.

Cause	N (%)
Trauma	44 (60)
Vascular insult	12 (16)
Opioids	8 (11)
Infection	5 (7)
Surgery	4 (5)
Intravenous-infiltration	1 (1)

**Table 1**

Characteristics of 74 patients with opioid-related or nonopioid-related compartment syndrome, 2016–2018.

Variable	Total (n = 74)			Opioid-related (n = 8)			Nonopioid-related (n = 66)			P
	N	Mean $\pm$ SD	Median (IQR)	N (%)	Mean $\pm$ SD	Median (IQR)	N (%)	Mean $\pm$ SD	Median (IQR)	
Female sex	18			0 (0)			18 (27)			0.07
Age (yr)		43 $\pm$ 15			38 $\pm$ 11			43 $\pm$ 16		0.42
BMI (kg/m <sup>2</sup> )		28 $\pm$ 6.1			29 $\pm$ 4.9			28 $\pm$ 6.3		0.86
Fasciotomies	75			9 (12)			66 (88)			
ASA class			2 (2–3)			3 (2.5–3.5)			2 (2–3)	<0.055
Peak CK (U/L)		4610 $\pm$ 10,800			224,000 $\pm$ 225,000			7550 $\pm$ 32,500		<0.001
CVVHD	10			7 (88)			2 (3.0)			<0.001
Compartments released										
>1	16			7 (88)			8 (12)			<0.001
1	59			1 (13)			58 (88)			
Debridement			3 (2–4)			4 (3–6)			3 (2–4)	<0.031
Amputation	2			2 (25)			0 (0)			0.013
Duration of hospital stay (d)			10 (5–19)			27 (16–38)			9 (5–13)	<0.001

ASA: American Society of Anesthesiologists; BMI: body mass index; CK: creatinine kinase; CVVHD: continuous venovenous-hemodialysis; IQR, interquartile range; U/L: units per liter.

**Table 3**  
Characteristics of 8 men with opioid-related compartment syndrome.

Patient No.	Age, yr	BMI, kg/m <sup>2</sup>	Compartments involved	Amputation (transfemoral)	Peak CK, U/L	CVVHD	iHD	No. of debridements	LOS, d
1	59	22.5	Thigh, gluteal	No	108,020	Yes	No	2	15
2	44	34.9	Leg, thigh	Yes	601,400	Yes	No	6	41
3	43	27.1	Leg (bilateral)	No	35,000	No	No	3	13
4	41	26.3	Thigh, gluteal	No	50,790	Yes	Yes	3	26
5	38	32.8	Leg	Yes	137,890	Yes	No	8	68
6	28	35.5	Leg (bilateral)	No	556,400	Yes	Yes	6	34
7	28	25.8	Leg, thigh, gluteal	No	198,380	Yes	No	5	28
8	26	24.9	Leg, gluteal	No	104,120	Yes	No	3	16

BMI: body mass index; CK: creatinine kinase; CVVHD: continuous venovenous-hemodialysis; iHD: intermittent hemodialysis on discharge; LOS: length of stay; U/L: units per liter.

days; IQR: 16–38 days) compared with the NORCS group (median, 9 days; IQR: 5–13) ( $p < 0.001$ ).

## Discussion

To our knowledge, ours is the first study to compare outcomes of patients with ORCS versus NORCS. Opioid abuse was the third most common cause of compartment syndrome. Notably, all ORCS patients presented after immobilization in a dependent position for at least 8 h. ORCS patients experienced greater morbidity during the perioperative hospitalization period compared with NORCS patients. Additionally, ORCS patients had significantly higher rates of muscle breakdown, hemodialysis, repeat debridement, and amputation, as well as longer hospital stays than those with NORCS. All but 1 patient in the ORCS group underwent release of multiple compartments.

As evident in our patients, a prolonged period of immobilization can lead to increased pressure on specific extremities and should raise the index of suspicion for compartment syndrome. First responders, health care providers who initially evaluate patients suspected of having opioid overdose, should have a high index of suspicion for compartment syndrome, even when patients present without obvious insult or trauma but otherwise show evidence of evolving compartment syndrome.

Patients presenting with ORCS had high rates of rhabdomyolysis and subsequent renal failure requiring urgent and continuous hemodialysis. These rates likely reflect the mechanism of injury, as well as the frequent delay in presentation described in several case reports [10,14,17,20]. Patients with ORCS also had a significantly higher rate of urgent hemodialysis compared with the NORCS group, with an additional 25% of ORCS patients requiring dialysis after discharge. Many patients do not recover renal function and require intermittent hemodialysis and close monitoring after discharge from the hospital [5,9,12,14,21,24]. However, 75% of our patients were not dialysis-dependent at discharge. This finding may be attributable to the quick initiation of continuous hemodialysis, which has been shown to aid in clearance of nephrotoxic myoglobin and return of normal renal function [25].

The gluteal compartments are rarely affected by compartment syndrome, yet several case reports [7,14,16,17] and the study by Bennis et al. [5] have noted an increased frequency of gluteal compartment syndrome in patients who develop ORCS. This increase may be attributable to prolonged immobilization in a dependent position, such as being prone or seated [26]. Similarly, 5 of our 9 patients with ORCS underwent gluteal compartment fasciotomies. Given the higher rate of gluteal compartment syndrome observed in patients with opioid overdose compared with NORCS, clinicians should evaluate the gluteal compartments in these patients.

ORCS was associated with a higher risk of amputation than was NORCS. The prolonged time between initiation of compartment syndrome symptoms (likely before hospitalization) and diagnosis

likely increases the risk of tissue necrosis and need for amputation. Clinicians should have a high index of suspicion for compartment syndrome in unconscious patients. Additionally, such patients may need to be counseled on the poor prognosis of their injury.

The primary limitation of this study was its retrospective design. Additionally, the dataset was derived from billing codes, and some cases may have been coded incorrectly. Finally, the number of ORCS cases was low, preventing us from performing multivariable analyses. However, this is the first study, to our knowledge, to compare inpatient outcomes between patients with ORCS versus NORCS.

## Conclusion

Patients who developed compartment syndrome secondary to opioid overdose were more likely to have delayed presentation, rhabdomyolysis, and kidney failure requiring dialysis than were patients with compartment syndrome from other causes. Additionally, patients with ORCS had more extensive involvement of their compartments, more extremities involved, and more debridements and amputations compared with patients with NORCS. Our results suggest that patients with ORCS are at high risk for the disabling sequelae of compartment syndrome.

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## Declaration of competing interest

The authors have no conflicts of interest to report.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.injury.2019.06.013>.

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