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REVIEW

Regional anesthesia or patient-controlled analgesia and compartment syndrome in orthopedic surgical procedures: a systematic review

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Elizabeth BS Driscoll[1]
Ana Hosseinzadeh Maleki[2]
Leila Jahromi[3]
Brittany Nelson Hermecz[4]
Lauren E Nelson[5]
Imelda L Vetter[6]
Spencer Evenhuis[2]
Lee Ann Riesenberg[2]

[1]Department of Anesthesiology, University of Tennessee, Knoxville, TN, [2]Department of Anesthesiology and Perioperative Medicine, University of Alabama at Birmingham, Birmingham, AL, [3]Department of Biology, Georgia State University, Atlanta, GA, [4]Department of Diagnostic Radiology, University of Alabama at Birmingham School of Medicine, Birmingham, [5]University of South Alabama College of Medicine, Mobile, [6]School of Health Professions, Lister Hill Library, University of Alabama at Birmingham, Birmingham, AL, USA

Correspondence: Elizabeth BS Driscoll
Department of Anesthesiology, University of Tennessee, U109, 1924 Alcoa Highway, Knoxville, TN 37920-1511, USA
Tel +1 865 305 9220
Fax +1 865 305 9216
Email edriscoll@utmck.edu

Abstract: A systematic review of the literature on the use of regional anesthesia (RA) and patient-controlled analgesia (PCA) was conducted in patients who require orthopedic extremity procedures to determine whether either analgesic technique contributes to a delayed diagnosis of compartment syndrome (CS). A total of 34 relevant articles (28 case reports and six research articles) were identified. Of all case report articles published after 2009, the majority (75%) concluded that RA does not put the patient at an increased risk of a delayed diagnosis of CS. Of these, only two relevant prospective research studies focusing on RA or PCA and their relationship to CS were identified. Neither study resulted in any cases of CS. However, both had relatively small sample sizes. Given the lack of evidence identified in this systematic review, prospective studies or large-scale retrospective data reviews are needed to more strongly advocate the use of one modality of analgesia over the other in this patient population.

Keywords: compartment syndrome, patient-controlled analgesia, regional anesthesia, peripheral nerve block

Introduction

Acute compartment syndrome (CS), a true medical emergency, is a rare, yet serious complication of certain injuries and operations.[1,2] It is a condition in which increased pressure within a confined, nonelastic space compromises the circulation and thus the function of the tissues within that space.[3] Early recognition and treatment with an emergent fasciotomy is crucial, as the risk of complications such as muscle necrosis,[4,5] neurological deficits,[3,5,6] delayed fracture union,[7] Volkmann ischemic contraction,[8] myoglobinuria,[8–10] renal failure,[8–12] and potentially death[10,11,13] increases as time of tissue anoxia elapses.[14–17] The diagnosis of CS is clinical and requires a high index of suspicion.[6,18,19] Classical symptoms of CS include pain,[13,20–25] pallor,[25,26] paresthesias,[20,24,25,27] pulselessness,[24] and paralysis.[23,24] Of these cardinal signs and symptoms, pain is believed to be one of the first clinical indicators of an impending CS.[11,24,28,29] Specifically, when a patient experiences pain that is progressive, not relieved by narcotics, out of proportion to examination, and with passive motion, the clinician should be attuned to the possibility of CS.[13,21,24] Regional analgesia or regional anesthesia (RA) is often used to alleviate pain in patients who have had limb injuries or interventions.[1,30,31] RA has

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long been the accepted practice for providing postoperative pain control in elective orthopedic procedures, particularly total joint arthroplasties, despite the risk of CS.[32,33] There are several benefits to using RA in these patients, such as better pain control,[1,34] saving time and costs due to shorter hospital stays and fewer nursing interventions,[32] and sparing patients the adverse effects of systemic opioids[32] and general anesthesia.[1] However, some argue that RA masks the ischemic pain associated with CS[32,35–37] and therefore delays the diagnosis, putting the patient at greater risk for complications.[3,38]

Patient-controlled analgesia (PCA) is a widely accepted technique for orthopedic postoperative pain management,[38–40] despite the risk of CS development. The main advantage of this technique is that patients control their own dosing.[40,41] PCA provides better matching of patient need with analgesia and avoids opioid overdose and side effects.[41] However, it has also been argued that PCA may mask the symptoms of CS and potentially delay the diagnosis.[38–40]

Some physicians dispute the use of RA in orthopedic injuries, believing that this modality poses a greater risk than PCA for masking the signs/symptoms of CS.[24] Given this controversy, we decided to conduct a systematic review of the literature to compare the two pain control modalities (RA and PCA). Specifically, we set out to compare their contribution to a delayed diagnosis of CS in traumatic and elective orthopedic cases.

In our initial search, we identified 19 relevant review articles published between 1999 and 2014,[19,23,24,27,31,42–55] with three of these being case reports that included literature reviews.[43,47,51] However, none followed the currently accepted rigorous guidelines for conducting systematic reviews of the literature, including teams of reviewers or an iterative abstraction process.[56–59] In addition, none answered our primary question as to whether RA or PCA contributes to a delayed diagnosis of CS in traumatic and elective orthopedic cases. Thus, we proceeded with a systematic review of the literature.

Methods

Literature search

We conducted a thorough and systematic review of English language literature published on the use of RA or PCA in orthopedic cases involving extremity surgeries and that include CS, between January 1, 1980, and November 2014 using CINAHL, PubMed, and Scopus.

For the searches, we chose relevant controlled vocabulary and keywords to capture the concepts of RA or PCA "and" CS (complete details of the search strategy are available upon request from the authors, or in Table 1). The search strategy identified 471 unique articles (478 total, with seven duplicates).

All titles were reviewed by two teams of trained reviewers for possible inclusion (EBSD and BNH; LJ and AHM). Prior

Table 1 Literature search methods and results for a systematic review of RA or PCA and CS

Number of search results					
Database	**Platform**	**Date of search**	**Date limits**	**Other limits**	**Total references**
PubMed	NLM	April 8, 2014	1980–2014	English, age of the study participants: ≥13 years	136
CINAHL	EBSCO	April 16, 2014	1980–2014	English, age of the study participants: ≥13 years	30
Scopus	Elsevier	April 28, 2014	1980–2014	English, cannot limit for the age of the study participants in this database	114
Scopus[a]	Elsevier	May 27, 2014	1980–2014	English, cannot limit for the age of the study participants in this database	414
PubMed	NLM	November 21, 2014	1980–2014	English, did not limit for the age of the study participants	217
CINAHL	EBSCO	November 21, 2014	1980–2014	English, did not limit for the age of the study participants	56
Scopus	Elsevier	December 12, 2014	2014	English, cannot limit for the age of the study participants in this database	21
PubMed	NLM	December 12, 2014	2014	English, did not limit for the age of the study participants	9
CINAHL	EBSCO	December 12, 2014	2014	English, did not limit for the age of the study participants	5
Total					1,002

Topic-specific search terms

Concept	Controlled vocabulary	Keywords
CS	CSs (MeSH)	Compartment Syndrome
	Anterior CS (MeSH)	Syndrome, Compartment
		Syndromes, Compartment
	Ischemic contracture (MeSH)	Syndrome, Anterior Compartment
		Syndromes, Anterior Compartment
		Anterior Tibial Syndrome
		Syndrome, Anterior Tibial
		Syndromes, Anterior Tibial
		Volkmann's Contracture
RA	Anesthesia, regional (MeSH)	Anaesthesia, Regional
	Anesthesia, conduction (MeSH)	Regional Anesthesia
	Anesthesia, epidural (MeSH)	Regional Anaesthesia
	Anesthesia, spinal (MeSH)	Anaesthesia, Conduction
	Anesthesia, local (MeSH)	Conduction Anesthesia
	Nerve block (MeSH)	Conduction Anaesthesia
	Autonomic nerve block (MeSH)	Anaesthesia, Epidural
	Analgesia (MeSH)	Epidural Anesthesia
	Audioanalgesia (MeSH)	Epidural Anaesthesia
	Diffuse noxious inhibitory control (MeSH)	Anaesthesia, Spinal
		Spinal Anesthesia
	Neuroleptanalgesia (MeSH)	Spinal Anaesthesia
	Transcutaneous electric nerve	Anaesthesia, Local
	Stimulation (MeSH)	Local Anesthesia
	Electroacupuncture (MeSH)	Local Anaesthesia
		Nerve Block Catheter
		Block
		Bier Block
		Peripheral Nerve Block
		Peripheral Nerve Blockade
		Femoral Nerve Block
		Brachial Plexus Block
		Paravertebral Block
		Sciatic Nerve Block
		Popliteal Nerve Block
		Postoperative Anesthesia
		Postoperative Anaesthesia
		Anesthesia, Postoperative
		Anaesthesia, Postoperative
		Postoperative Analgesia
		Analgesia, Postoperative
		Epidural
		IV PCA
		Intravenous PCA
		Intravenous Patient Controlled Analgesia*
		Patient Controlled Analgesia
		Patient Controlled Anesthesia
		Patient Controlled Anaesthesia
		IV Sedation
		Intravenous Sedation
		Narcotic
		Opioid
		Morphine
		Dilaudid
		Fentanyl
		Ropivacaine
		Bupivacaine
		Lidocaine
		Analgesias

(*Continued*)

Table 1 (*Continued*)

Topic-specific search terms		
Concept	**Controlled vocabulary**	**Keywords**
		Anesthesia, Infiltration
		Infiltration Anesthesia
		Anaesthesia, Infiltration
		Infiltration Anaesthesia
Set number	**Search statement**	
Search strategy: search term 1 (concept = CS)		
1	Compartment Syndromes	
2	Compartment Syndrome	
3	Ischemic Contracture	
4	Anterior Compartment Syndrome	
5	Syndrome, Compartment	
6	Syndromes, Compartment	
7	Syndrome, Anterior Compartment	
8	Syndromes, Anterior Compartment	
9	Anterior Tibial Syndrome	
10	Syndrome, Anterior Tibial	
11	Syndromes, Anterior Tibial	
12	Volkmann's Contracture	
13	OR/1–12	
Search strategy: search term 2 (concept = RA)		
14	Regional Anesthesia	
15	Regional Anaesthesia	
16	Anesthesia, Regional	
17	Anaesthesia, Regional	
18	Conduction Anesthesia	
19	Conduction Anaesthesia	
20	Anesthesia, Conduction	
21	Anaesthesia, Conduction	
22	Spinal Anesthesia	
23	Spinal Anaesthesia	
24	Anesthesia, Spinal	
25	Anaesthesia, Spinal	
26	Anesthesia, Epidural	
27	Anaesthesia, Epidural	
28	Epidural Anesthesia	
29	Epidural Anaesthesia	
30	Local Anesthesia	
31	Local Anaesthesia	
32	Anesthesia, Local	
33	Anaesthesia, Local	
34	Spinal Anesthesia	
35	Spinal Anaesthesia	
36	Anesthesia, Spinal	
37	Anaesthesia, Spinal	
38	Postoperative Anesthesia	
39	Postoperative Anaesthesia	
40	Anesthesia, Postoperative	
41	Anaesthesia, Postoperative	
42	Infiltration Anesthesia	
43	Infiltration Anaesthesia	
44	Anesthesia, Infiltration	
45	Anaesthesia, Infiltration	
46	Analgesia*	
47	Block	
48	Audioanalgesia	
49	Epidural	

Set number	Search statement
50	IV PCA
51	Intravenous PCA
52	Intravenous Patient Controlled Analgesia
53	Patient Controlled Anesthesia
54	Patient Controlled Anaesthesia
55	IV Sedation
56	Intravenous Sedation
57	Diffuse Noxious Inhibitory Control
58	Neuroleptanalgesia
59	Transcutaneous Electric Nerve
60	Simulation
61	Electroacupuncture
62	Narcotic
63	Opioid
64	Morphine
65	Dilaudid
66	Fentanyl
67	Ropivacaine
68	Bupivacaine
69	Lidocaine
70	OR/14–69
71	(13 AND 70)
72	71 AND English language AND 1980–2014 AND Ages ≥13

Notes: [a]The Scopus search conducted on April 28, 2014, was with the "Document Search" (basic search) function; this function truncates long strings of search terms. Thus, we reran the search on May 27, 2014, with the "Advanced Search" function, so that there would be no truncation of search terms. After de-duplicating the 1,002 results, there were 475 unique articles. Database conventions: *, truncation; "", phrase searching; [MeSH], medical subject heading; AND, OR, NOT, Boolean operators. In Scopus, there is no capability to restrict the age of the study participants. In PubMed, the author did not use truncation (via the * symbol), because the use of truncation turns off automatic mapping to MeSH terms.

Abbreviations: CS, compartment syndrome; IV, intravenous; NLM, National Library of Medicine; PCA, patient-controlled analgesia; RA, regional anesthesia.

to beginning the review, both reviewers agreed to err on the side of inclusion. If either reviewer selected a reference, the full text was ordered for further review. Using this strategy, 179 articles were obtained for further review. The percent agreement on initial independent selection of articles for further review was 86%. Interrater reliability using Cohen's kappa was κ=0.67, P<0.001. The reference sections of all included articles were checked for additional potentially relevant articles, with six being identified (Figure 1).

Inclusion and exclusion criteria

Articles meeting the following criteria were eligible for review: English language; published between January 1, 1980, and November 2014; focused on RA or PCA used after an orthopedic surgical procedure that also included CS in an extremity; patients aged 13 years or older; and all types of research studies and case reports. Exclusion criteria included pediatric cases aged 0–12 years of age; CS not in an extremity (ie, gluteal and abdominal) or resulting from the lithotomy position; orthopedic surgeries not involving the extremities; and letters, editorials, or commentaries.

Research studies and case reports

Teams of two independent researchers (LJ, AHM, BNH, and LEN) checked all articles for initial relevance and assigned each article to one or more categories: research study or case report. Then, a subgroup of the research team (EBSD, LAR, LJ, and AHM) met to review all included articles to determine the final inclusion and accuracy of category assignment.

Abstraction process

Trained reviewers used an iterative process to develop an abstraction form designed to confirm the final eligibility for full review, assess article characteristics, and extract data relevant to the study question. This iterative process started with two initial forms, one for case reports and one for research articles. Both forms were used by multiple reviewers (BNH, AHM, LJ, and LEN) to independently abstract data from the articles. The reviewers then met with their mentor for this study (LAR) to discuss the abstraction forms, to decide whether the form should be revised, and receive guidance related to any abstraction questions. More relevant forms were then created for abstraction. This iterative process continued until the team was confident that the abstraction forms had fields for all potentially relevant information and the team no longer had questions about abstraction of these articles.

Results

We identified 477 articles in our search and deemed 34 of them relevant to our study: 28 case reports (23 RA case

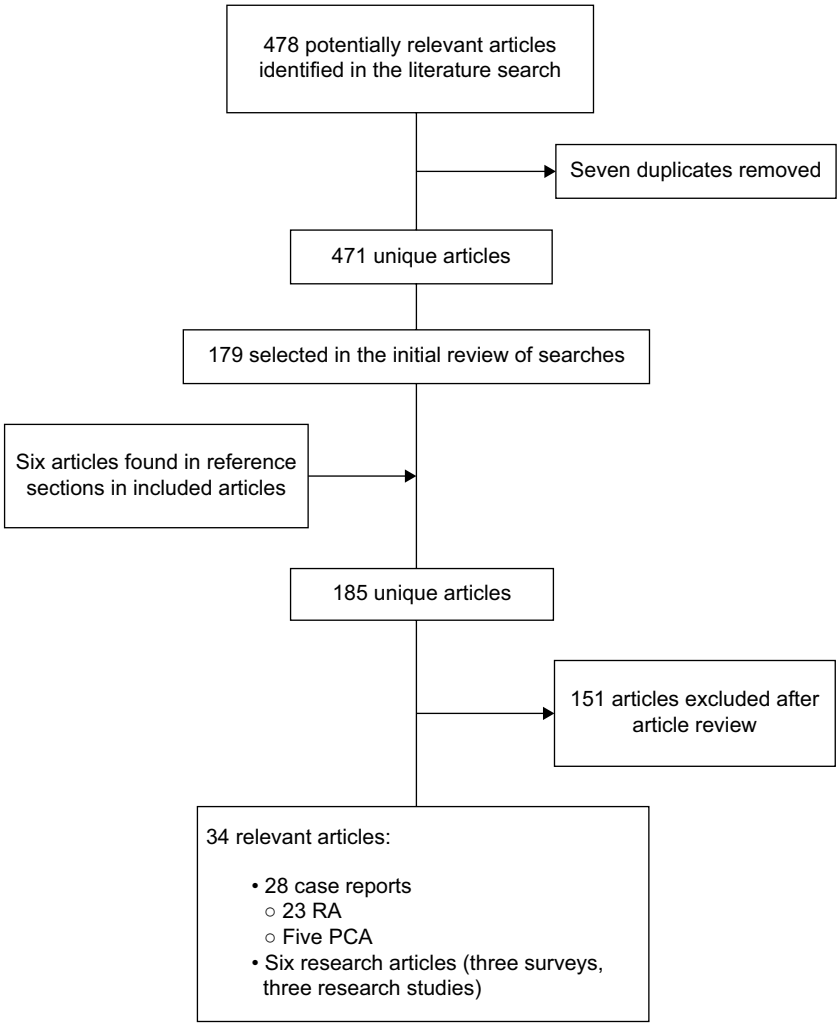

Figure 1 The process used during a systematic review of the literature to select articles (review, case reports, and research) on RA or PCA and CS.
Abbreviations: CS, compartment syndrome; PCA, patient-controlled analgesia; RA, regional anesthesia.

reports and five PCA case reports) and six research articles (three surveys and three research studies; Figure 1).

Research studies

We identified six relevant research studies (three survey and three research studies) published between 1989 and 2012.[11,60–64] Of six research studies, three (50%) authors concluded that the use of either RA or PCA does mask the symptoms of CS,[11,60,61] one (16.7%) concluded that RA does not mask the symptoms of CS,[62] and two (33.3%) were unclear or did not provide relevant conclusions.[63,64]

Three (50%) were survey studies conducted in the UK.[11,61,62] Davis et al[11] conducted a mail-in survey of the practices of 146 consultant and 97 non-consultant grade anesthetists. The majority, 81% and 91%, respectively, replied that they use RA in all lower extremity fractions and 17% and 9%, respectively, had personally witnessed CS masked by the RA. The authors raised concerns over these regional practices, some of which were reported to be in settings without adequate compartment pressure monitoring, though no specifics about the regional techniques, medications, or cases were discussed in the survey. Thonse et al[61] administered questionnaires with seven clinical vignettes describing patients undergoing surgery of an extremity (elective and trauma) to 190 orthopedic surgery and anesthetist trainees. Subjects were not aware that the study was focused on the risk of delayed diagnosis of CS. A total of 114 (60%) responded, 56 of which were orthopedic surgeons and 58 anesthesiologists. They found statistically significant differences between the two groups, with anesthetists preferring local and regional nerve blocks in patients known to have a high risk of CS. In 2009, Pennington et al[62] conducted a telephone survey of middle-grade physicians in 171 acute care hospitals providing trauma care. Questions focused on departmental protocols

and respondent experience with femoral nerve blocks for lower limb fractures. They achieved a 100% response rate and concluded that femoral nerve block is an underutilized, effective mode of analgesia following femoral fractures. Respondents reported a low incidence of CS, but urged vigilance in monitoring patients with high-energy injuries.

There were three (50%) studies conducted in the US.[60,63,64] One (33.3%) was a retrospective review conducted prior to 2000.[60] Iaquinto et al[60] reviewed 63 patients with surgical repair of a tibial fracture. These patients received postoperative epidural analgesia with local anesthetics. None of these patients developed CS.

There were two (66.7%) prospective studies.[63,64] Weller et al[63] conducted the only prospective randomized study comparing epidural to patient-controlled intravenous morphine following joint replacement (total hip and knee replacement) surgery. Half (15/30) received epidural morphine and the other half (15/30) received patient-controlled intravenous morphine. They followed patients for 24 hours, during which none of the patients developed CS. This prospective study focused on the pain control and side effects of the two delivery methods of morphine but has limited relevancy to our question as there were no cases of CS discovered. In addition, the postoperative follow-up focused on intravenous and epidural morphine use with the only local anesthetic used for short-term surgical anesthesia and not postoperative analgesia. Ganesh et al[64] prospectively followed 217 pediatric patients, 167 of whom were children aged ≥13 years and had continuous peripheral nerve blockade after orthopedic procedures. Again, none of these patients developed CS.

Case reports

We identified 28 case report articles published between 1986 and 2013: 23 RA articles, with 29 cases and five PCA articles, with eight cases (Tables 2 and 3). Of 23 RA articles, 13 (56.5%) authors (representing 19 cases) concluded that RA masked the symptoms of CS,[32,34–36,65–74] delaying the diagnosis. However, of these 19 cases, eleven (57.8%) presented with "pain" (± other symptoms).[32,35,65,67–70,74] In addition, while eight (42.1%) cases did not report pain, they did present with other classic symptoms of CS, such as paresthesia, altered sensation, swelling and edema, tense and shiny skin, loss of movement, or foot drop (Table 2).[36,66,71–73]

In the remaining ten RA articles described with all available details in Table 2, eight (80%) authors (representing eight cases) concluded that RA did not mask the symptoms of CS,[3,33,47,51,75–78] while two (20%) authors (representing two cases) provided unclear conclusions on this question.[20,79] Eight of the 23 RA articles (34.8%) were published between 2010 and 2013.[3,33,47,51,67,75,77,79] The majority of these more current articles (six of eight; 75%) did not conclude that RA masks symptoms of CS (Table 2).[3,33,47,51,75,77]

Of the five articles that describe the use of PCA, representing eight total cases detailed in Table 3, three (60%) of these authors (six cases) concluded that PCA does mask CS.[38–40] The other two authors (two cases) were unclear on this issue (Table 3).[80,81]

Overall, of the 28 combined (RA and PCA) case report articles (representing 37 cases), 22 cases (59.5%) presented with pain (± other symptoms).[3,32,33,35,38,47,51,65,67–70,74–76,78,79,80,81] In the remaining 15 cases (40.5%), patients did not present with pain but did present with other classic signs/symptoms of CS (Tables 2 and 3).[20,36,39,40,66,71–73,77]

The use of RA for trauma and orthopedic surgery remains controversial.[24,47,49–51,55] Of the reviewed articles, seven authors recommend that postoperative RA be used cautiously[65,75] or with a lower dose of local anesthetic[31,42,50,54,62] in patients who are at risk for the development of a CS, and five believe that nerve block should not be used when there is a possibility of a CS.[35,38,44,63,66] In addition, two authors support establishing a protocol or guidelines for the use of inpatient nerve blocks.[62,64]

Discussion

We conducted a systematic review of the literature on the use of either RA or PCA in orthopedic surgical cases of the extremities. Our goal was to objectively describe the current state of evidence relevant to RA and/or PCA and the development of CS. We identified 34 articles (28 case reports, three surveys, and three research studies). Of these, 19 (55.9%) concluded that RA or PCA does mask symptoms of CS,[1,32,35,36,38–40,60,61,65–74] nine (26.5%) concluded that RA or PCA does not mask symptoms,[3,33,47,51,62,75–78] and six (17.6%) were unclear.[20,63,64,79,81,82]

However, 25 articles (73.5%) were published between 1986 and 2009. One could argue that these earlier articles do not accurately reflect current practice. When looking only at eight case report articles published after 2009, the abovementioned percentages markedly change, with one (12.5%) concluding that RA or PCA does mask symptoms of CS,[67] six (75%) concluding that RA or PCA does not mask symptoms,[3,33,47,51,62,75,77] and one (12.5%) was unclear.[79] The change in attribution in more recent publications may be due to advances in ultrasound-guided nerve blocks, making these procedures more desirable as they are often quicker and less technically challenging.[83,84] Ultrasound-guided

Table 2 Case reports identified in a systematic review of the literature on RA and CS (23 articles, with 29 cases), 1980 to November 2014

Case report	Procedure	Age (years); sex; weight	RA	Medications at the time of diagnosis	Signs/symptoms	Treatment	Did RA mask CS?	Monitoring
Traumatic orthopedic procedures								
Aguirre et al[3]	Open repositioning of a complex distal right humerus fracture	47; female; not available	Infraclavicular nerve block catheter	Continuous 0.3% ropivacaine at 6 mL/h for an unreported length of time. An additional 20 mL bolus of 0.5% ropivacaine was administered at the time when patient developed increasing pain	Severe pain	Fasciotomy	No	Physical examination and compartment pressure measurement of 40 mmHg
Azam et al[67]	Surgical stabilization of bilateral femur fractures and both bone right leg fractures	32; male; not available	Epidural analgesia	3 mg morphine in 10 mL normal saline every 12 hours	Four hours after the removal of epidural catheter, patient started complaining of progressive pain unrelieved by appropriate oral analgesic. Clinical examination revealed swollen compartment of leg with altered sensorium and significant pain on passive stretching. Extension of toe and dorsiflexion of ankle was remarkably absent. Dorsalis pedis was not palpable and posterior tibial artery was doubtful. Nail bed circulation was present	Fasciotomy	Yes	Physical examination and compartment pressure measurement (unknown)
Hyder et al[66]	Closed fracture of tibial shaft with intramedullary nailing	28; male; not available	Triple nerve block (femoral, obturator, lateral cutaneous nerve of thigh)	0.5% bupivacaine	Postoperatively, the patient had altered sensation in the foot and leg. At 48 hours postoperatively, these symptoms persisted, and the patient was unable to actively extend the big toe	Fasciotomy	Yes	Physical examination and compartment pressure measurement of 108 mmHg
Morrow et al[36]	Intramedullary nailing of the tibia	18; male; not available	Epidural anesthesia	Initial bolus of 50 μg fentanyl and 50 mg bupivacaine, and epidural fentanyl (10 μg/mL) and bupivacaine (2 mg/mL) at 4 mL/h employed overnight	At 13 hours postoperatively, the patient experienced total anesthesia and paresis of the left leg. Left calf muscle turgidity was observed	Fasciotomy	Yes	Physical examination and compartment pressure measurement of 70 mmHg
Patillo et al[75]	Closed reduction in pilon fracture with application of an external fixator spanning	19; male; not available	Epidural anesthesia	Not available	48 hours after the initial injury, the patient awoke with severe right leg pain that was poorly controlled with both epidural and oral narcotic pain medication, also severe pain with passive range of motion of the great toe and some mild paresthesias over the dorsum of the foot. Capillary refill throughout the foot was <3 seconds on each examination	Fasciotomy	No	Physical examination and compartment pressure monitoring (peaked at 48 mmHg)
Uzel and Steinmann[68]	Closed femoral fracture internal fixation using an intramedullary rod	26; male; 66 kg	Femoral nerve block	Single injection with 20 mL 0.75% ropivacaine hydrochloride	Patient complained of unusually severe pain. The anterior thigh compartment was very taut, and there was no sensorimotor or vascular deficit	Fasciotomy	Yes	Physical examination and compartment pressure measurement of 54 mmHg

Elective total joint arthroplasties								
Bezwada et al[20]	Bilateral consecutive TKA for tri-compartmental osteoarthritis of both knees	60; male; not available	Epidural anesthesia	Bupivacaine and fentanyl	Reduced strength and active movement of the right foot, numbness, edema, and ecchymoses	Fasciotomy	Unclear	Compartment pressure monitoring (peaked at 30 mmHg)
Haggis et al[32]	Revision of left TKA	69; female; not available	Epidural anesthesia	Not available	Edema (no pain)	Fasciotomy	Yes	Physical examination
Haggis et al[32]	Right TKA in a patient with the history of chronic osteomyelitis of right femur and tibia, septic arthritis of right knee	53; male; not available	Epidural anesthesia	Not available	Pain, coldness, pulselessness, edema	Fasciotomy	Yes	Physical examination
Haggis et al[32]	Right TKA in a patient with valgus osteoarthritis	48; female; not available	Epidural anesthesia	Not available	Swelling, foot drop	Fasciotomy	Yes	Physical examination
Haggis et al[32]	Right TKA in a patient with epiphyseal dysplasia. Right knee arthrodesis (before 16 years). This was a conversion to TKA	39; female; not available	Epidural anesthesia	Not available	Pain, pulselessness, edema	Fasciotomy	Yes	Physical examination
Haggis et al[32]	Left TKA	49; female; not available	Epidural anesthesia	Not available	Pain, foot drop	Fasciotomy	Yes	Physical examination and compartment pressure monitoring (peaked at 94 mmHg)
Haggis et al[32]	Right TKA	61; male; not available	Epidural anesthesia	Not available	Pain, paralysis, paresthesia, edema	Fasciotomy	Yes	Physical examination
Hailer[35]	TKA	43; female; not available	Epidural anesthesia	Epidural infusion of ropivacaine and sufentanil, later IV ketobemidone	Loss of active toe extension, pain, pulselessness, edema	Fasciotomy	Yes	Physical examination

(*Continued*)

Table 2 (*Continued*)

Case report	Procedure	Age (years); sex; weight	RA	Medications at the time of diagnosis	Signs/symptoms	Treatment	Did RA mask CS?	Monitoring
Kort et al[76]	TKA	44; female; BMI, 39 kg/m^2	Epidural anesthesia	0.125% bupivacaine at a rate of 8 mL/h	The peripheral pulses were not palpable on the operated leg, but the capillary refill was normal. Approximately 12 hours postoperatively, the patient complained of pain and swelling in the left leg. There were normal neurologic findings, and the capillary refill was also normal. The pain was worsened by passive stretch of the involved muscles	Fasciotomy	No	Physical Examination
LaReau et al[79]	TKA	73; male; not available	Femoral nerve block	30 mL of 0.375% bupivacaine with epinephrine at a concentration of 1:400,000	On the evening of postoperative day 1, nursing reported increasing pain and difficulty with the range of motion	Fasciotomy	Unclear	Physical examination and compartment pressure monitoring (as high as 50 mmHg)
Nicholl et al[69]	Revision total hip arthroplasty	65; male; not available	Epidural anesthesia	Epidural morphine infusion	At 24 hours postoperatively, the patient complained of pain in the left lower shin, which was swollen and tender. Active and passive movements of the ankle and toes produced some discomfort. At 72 hours postoperatively, the leg was more swollen, tense, and painful, with paresthesia in the foot	Fasciotomy	Yes	Physical examination and compartment pressure monitoring (peaked at >32 mmHg)
Noorpuri et al[70]	Revision arthroplasty of the forefoot	37; female; not available	Ankle block	Ankle block was performed to the sural, saphenous, anterior, and posterior tibial nerves using 30 mL 0.25% bupivacaine	Breakthrough pain, edema, paresthesia, altered sensation, delayed capillary refill, reduced active movement of toes, exaggerated pain with passive motion	Fasciotomy	Yes	None
Tang and Chiu[71]	TKA	62; female; not available	Epidural anesthesia	Continuous 0.125% bupivacaine at the rate of 8 mL/h	On postoperative day 2, the capillary return of right toes diminished. Toes were also swollen	Fasciotomy	Yes	Physical examination and compartment pressure measurement (peaked at 80 mmHg)
Other elective orthopedic procedures								
Addison et al[72]	Extensive resection of osteosarcoma and closure of the anterolateral thigh flap	25; male; not available	Epidural anesthesia	Not available	On the third postoperative day, the donor site wound margins were noted to be blistering, tense, and moist. The patient was noted to have a mildly swollen right leg, but no associated pain or skin changes	Operative debridement	Yes	Physical examination

Addison et al[72]	Resection of osteosarcoma and closure of the anterolateral thigh flap	38; male; not available	Epidural anesthesia	Not available	Five days after the procedure, the patient was noted to have some blistering and marginal necrosis of the thigh wound edges, but with no increase in pain. Over the next few days, the wound edges slowly worsened	Operative debridement	Yes	Physical examination
Chidambaran et al[77]	Left knee multi-ligamentous reconstruction	16; male; BMI, 35 kg/m^2	Femoral and sciatic nerve block	Postoperative analgesia with 0.2% ropivacaine	On postoperative day 1, patient developed loss of ankle dorsiflexion, cola-colored urine and increased CPK	Physical therapy and forced alkaline dieresis	No	Thigh compartment pressure was high but did not warrant fasciotomy
Cometa et al[33]	Patient with Blount's disease underwent elective distal femur and proximal tibial osteotomy	15; male; 150 kg	Continuous femoral and sciatic nerve blocks	Femoral and sciatic nerve catheter infusions of 0.2% ropivacaine at 10 mL/h, decreased to 5 mL/h in femoral nerve catheter and 10 mL/h in sciatic nerve catheter	At >48 hours postoperatively, patient experienced pain (refractory to nerve blocks and IV opioids) that intensified with passive movement, edema, limitation in active movement of the foot, and weakness	Fasciotomy	No	Physical examination and compartment pressure monitoring (peaked at >30 mmHg)
Dunwoody et al[78]	Innominate triple osteotomy for developmental dysplasia of the left hip	14; male; 60 kg	Lumbar epidural anesthesia	Epidural infusion of fentanyl (1 μg/kg per hour) and bupivacaine (0.1%; 0.2 mg/kg per hour)	At 30 hours postoperatively, patient experienced exquisite pain with foot inversion and eversion, weak active dorsiflexion and plantar flexion of the toes, and weak ankle movement	Fasciotomy	No	Physical examination and compartment pressure monitoring (peaked at 45 mmHg)
Kucera and Boezaart[51]	Right lateral ankle ligament reconstruction for ankle instability	29; male; 85 kg	Single-injection sciatic and femoral nerve blocks	30 mL 0.5% ropivacaine sciatic; 20 mL 0.75% ropivacaine femoral	Pain, erythema	Cast removal	No	Physical examination
Price et al[73]	Left simultaneous corrective osteotomies of the femur and tibia	16; male; not available	Epidural anesthesia	Fentanyl	Paresthesia, swelling, tense and shiny skin	Fasciotomy	Yes	Physical examination and compartment pressure monitoring (peaked at 68 mmHg)
Seybold and Busconi[74]	Scapular fasciocutaneous-free flap grafting for a non-healed ulcer of the medial heel	18; male; not available	Epidural anesthesia	Not available	12 hours postoperatively, the patient's right anterior thigh was obviously swollen. 2 hours later, he experienced discomfort in his thigh and exquisite pain with active and passive flexion of the thigh	Fasciotomy	Yes	Physical examination and compartment pressure monitoring (peaked at 40 mmHg)
Strecker et al[65]	Osteocutaneous-free fibula transfer from right leg	45; male; not available	Epidural anesthesia	Continuous bupivacaine 0.125% at the rate of 10 mL/h	Dull pain improved by releasing bandage, dysesthesia, swelling, pain out of proportion to that expected from the procedure	Fasciotomy	Yes	Physical examination

(*Continued*)

Table 2 (*Continued*)

Case report	Procedure	Age (years); sex; weight	RA	Medications at the time of diagnosis	Signs/symptoms	Treatment	Did RA mask CS?	Monitoring
Walker et al[41]	Left calcaneal lengthening osteotomy and percutaneous Achilles tendon lengthening	19; female; 79 kg	Popliteal catheter and a single-injection saphenous nerve block at the mid-femur level	Popliteal catheter and single-injection saphenous nerve block in popliteal catheter: Initial bolus of 5 mL bupivacaine given, continuous infusion of ropivacaine 0.2% at 8 mL/h. In saphenous block, 5 mL bupivacaine 0.5% with 1:200,000 epinephrine; infusion turned down to 6 mL/h next day	Pain, tightness, decreased sensation	Cast splitting and use of a spacer	No	Physical examination

Abbreviations: BMI, body mass index; CPK, creatine phosphokinase; CS, compartment syndrome; IV, intravenous; RA, regional anesthesia; TKA, total knee arthroplasty; h, hour.

Table 3 Case reports identified in a systematic review of the literature on PCA and CS (five articles, with eight cases), 1980 to November 2014

Case report	Procedure	Age (years); sex; weight	Drug(s)	Signs/symptoms	Treatment	PCA masked CS?	Monitoring
Traumatic orthopedic procedures							
Harrington et al[40]	Isolate, open oblique fracture of mid-shaft of tibia; wound dressed and fracture splinted, then undreamed intramedullary nailing	53; male; 83 kg	PCA syringe pump provided bolus dose of 1 mg with a lock-out duration set at 5 minutes (maximum possible dose of 48 mg morphine in 4-hour period); 131 mg morphine was used over 36 hours postoperatively	Firm and swollen calf	Fasciotomy	Yes	Physical examination and compartment pressure measurement (peaked at 50 mmHg+) in four compartments of the leg, diastolic pressure of 75 mmHg
O'Sullivan et al[38]	Intramedullary nailing for closed, displaced mid-shaft fracture of tibia and fibula as well as calcaneal traction	21; male; not available	90 mg morphine through PCA (PCA device with 120 mg morphine and 2.5 mg droperidol in 50 mL normal saline; a bolus of 1 mg was available at 5-minute intervals; no background infusion); 75 mg diclofenac intramuscularly administered 12 hours postoperatively; PCA discontinued at 27 hours postoperatively	Numbness in toes, but able to move toes satisfactorily; drowsiness; severe, pounding pain in right leg after discontinuing PCA, and pain aggravated by passive dorsiflexion; decreased sensation all over right foot	Fasciotomy; limb amputation	Yes	Not available

Richards et al[39]	Closed, reamed intramedullary nailing of tibial shaft fractures	28; male; not available	10 mg of morphine through PCA	Extremely tense calf and obvious foot drop; dorsiflexion of foot and toes produced mild discomfort	Fasciotomy	Yes	Not available
Richards et al[39]	Closed, reamed intramedullary nailing	27; male; not available	13 mg morphine through PCA	Increasing inability to move toes; extremely tense calf; altered sensation over dorsum of foot but palpable pulse was noted; compartment pressure reading of 40 mmHg	Fasciotomy	Yes	Physical examination and compartment pressure measurement of 40 mmHg
Richards et al[39]	Reamed intramedullary nailing to fix displaced oblique diaphyseal fracture of the tibia	20; male; not available	15 mg morphine on demand through PCA	Altered sensation 16 hours postoperatively over dorsum of the foot; tense and swollen calf with pressure exceeding 50 mmHg	Fasciotomy	Yes	Physical examination and compartment pressure measurement of 50 mmHg
Richards et al[39]	Reamed intramedullary nailing to correct oblique displaced diaphyseal tibial fracture	26; male; not available	17 mg morphine through PCA	Tense calf 18 hours postoperatively with altered sensation over the dorsum of the foot	Fasciotomy	Yes	Not available
Elective orthopedic procedures							
Bae et al[83]	Postoperative/ radioulnar osteotomy	14.9; female; not available	Increasing dose of morphine from 1 mg to 2 mg (100% PCA) and increasing frequency of analgesia from every 6 hours to every 4 hours (50%)	Increasing pain and analgesia requirement, pallor, pulselessness, paresthesia, paralysis	Fasciotomy	Unclear	Physical examination
Mai[81]	Primary cemented total arthroplasty of the right hip joint	60; male; not available	IV morphine	Acute persistent right hip pain radiating to the right thigh and knee and not relieved with acetaminophen or IV morphine; on examination, the right thigh was markedly edematous and tender without neurovascular impairment	Fasciotomy	Unclear	Compartment pressure measurement of 62 cm H_2O (patient BP was 180/90 mmHg)

Abbreviations: BP, blood pressure; CS, compartment syndrome; IV, intravenous; PCA, patient-controlled analgesia.

techniques often result in a decreased volume of local anesthetic required to achieve a successful regional block.[85,86] In addition, the risk of misdiagnosing CS may be reduced by using continuous RA techniques, with decreased local anesthetic concentrations and using newer local anesthetics drugs.[27,33,87] Some authors have noted that ischemic pain is different from nociceptive pain, temperature discrimination, or neuropathic pain, and ischemic pain should not be masked when using RA, even with complete sensory and motor blockade.[51]

Only two (5.9%) of the 34 identified articles were relevant prospective research studies, and neither of these reported any cases of CS.[63,64] Despite this finding, there are possible design issues with these studies. Both had small sample sizes, which leaves open the possibility that they were underpowered to identify a difference. CS incidence has been shown to be 3.1 per 100,000, which makes CS a relatively rare event.[3,16] A larger sample size would be required to ensure that a negative study is adequately powered. Most importantly, neither project was specifically designed to look at CS as an end point, but instead reported the lack of any CS cases as a secondary outcome. Thus, these articles were discovered with our literature search despite their only marginal relevance to our question of whether certain anesthesia techniques delay the diagnosis of CS.

On the other hand, a large prospective pediatric study does exist that supports RA.[82] This article was excluded from our systematic review based on our age criterion (≥13 years). But its conclusions are relevant, given the paucity of evidence in adult studies. Llewellyn and Moriarty[82] conducted a large prospective audit of pediatric patients with more than 10,000 epidurals, concluding that "[t]he occurrence of compartment syndrome does not appear to be masked by the presence of working [epidural infusion analgesia]."

It is evident from our systematic review that there is no clear evidence to support the use of one modality of analgesia over the other with regard to a lessened risk of developing CS. Of the cases that we deemed relevant to our study, the authors only suggested that a given modality either did or did not put the patient at greater risk of developing CS without giving objective means for drawing their conclusions. Still others did not draw a clear conclusion, and some debated whether better monitoring could have prevented the development of CS (Tables 2 and 3).

Some authors advocate for lower concentrations of local anesthetics in regional blockade, which might provide analgesia while improving the detection of CS.[31,42,50,54,62] Others advocate improved monitoring.[19,27,36,39,65,67,68,71] This could include increased involvement of the RA team in postoperative care,[31,49,76] more screening of compartment pressure[35,37,65,66] using advanced noninvasive techniques,[53] and increased frequency of nursing neurovascular checks.[34,48]

In addition, recommendations published in 2010 by British military leadership, stated that clinicians in the field should be encouraged to use regional analgesic techniques in limb trauma.[88] This recommendation was based on a review of their historical data that found that the majority of CS cases were identified.[88]

Limitations

The current study is limited by the search strategy used. Specifically, the search terms we identified may not have included every relevant term. Nonetheless, the quality of our systematic review was strengthened by the development of a study protocol at the outset, which included an explicit search strategy and clear inclusion/exclusion criteria. In addition, our search was conducted by a master's prepared librarian who searched multiple databases, and we reviewed the reference sections of all included articles. Although our strategy minimizes the risk of missing germane articles, it does not eliminate the possibility.

The study question simply cannot be answered with case reports. Scientific inferences cannot be derived from the latter, as the conclusions inevitably contain some biases stemming from the authors and journals. For instance, all case reports that reported that RA masked CS[32,35,36,65,66,68–74] were published in surgical journals. Interestingly, most reports that defended RA[3,33,47,51,77] were published in anesthesiology or pain journals.

Unfortunately, the published literature on this topic identified by our review included only six research studies. In addition, three of these were surveys and the other three were heterogeneous in their methodology and populations. As a result, the evidence is weak at best. Finally, one would expect a highly concentrated RA infusion to have a greater chance of masking CS than a dilute infusion. However, due to the small number of actual research studies, we were not able to address this question.

Our exhaustive systematic review included a search that ended in November 2014. A simple PubMed search using our keywords to date of manuscript submission identified six additional articles that have been published from November 2014 until submission. One is a case report of a 4-year-old boy which would have been excluded from our search based on age.[89] Two others were case reports on adults, one with

an upper extremity nerve block for distal radius fracture that did not delay the diagnosis of CS and the other a total knee arthroplasty that had an epidural for postoperative pain control that was removed after 24 hours who had CS diagnosed after 48 hours.[90,91] Pinheiro et al[91] states that though the epidural described above contributed to the delayed diagnosis of CS, it was not the sole cause of the delay.

The PubMed search from November 2014 until submission date resulted in three additional articles, two review articles and one practice advisory. Gadsden and Warlick[92] in their review article discuss the use of RA in traumatic extremity injuries and summarized that peripheral nerve blocks do not appear to contribute to a delayed diagnosis of CS while advocating for prudent use of blocks and extra vigilance when they are used. Although a pediatric review article, Muhly et al[93] additionally comment that there is "theoretical evidence" that peripheral regional techniques do not hide the ischemic pain symptom of CS and that blocks can be safely used in their pediatric population with appropriate attentiveness and monitoring. The practice advisory was published in September 2015 by the European Society of Regional Anaesthesia and Pain Therapy and the American Society of Regional Anesthesia and Pain Medicine regarding controversial topics in pediatric pain medicine, including RA and CS. Although another pediatric-focused article that does not fit within the scope of our systematic review, it is important to note that these societies advocate for the use of regional anesthetic techniques in pediatric orthopedic procedures and outlines six "best practice rules" for its use, which includes use of reduced concentrations of local anesthetics, reducing the volume of local anesthetics in high-risk surgeries such as those involving the tibial compartment, using caution with additives in blocks, and close follow-up by a pain service with easily accessible compartment pressure monitoring.[94]

Currently, there are no clear recommendations regarding the use of RA in adult patients with orthopedic extremity procedures who are at increased risk of developing CS.[11,27,95] In addition, our search identified cases and opinions suggesting that PCA contributes to a delayed diagnosis of CS. Thus, more studies are needed. Randomized prospective trials may not be appropriate given the lack of convincing evidence and the ongoing controversy regarding the safety of RA in this at-risk population. However, the widespread use of computerized medical records today makes large-scale data mining feasible. This would allow for retrospective data analysis, reviewing all cases of CS, as well as prospective comparison of similar orthopedic practices that use different analgesic techniques.

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The authors report no conflicts of interest in this work.

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