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Case Report

Dexmedetomidine Infusion for the Management of Opioid-Induced Hyperalgesia

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Abstract

Objective. Understanding the actions of opioids now encompasses pronociceptive as well as antinociceptive mechanisms. Opioid-induced hyperalgesia (OIH) refers to increased pain sensitivity due to high-dose or prolonged opioid exposure. It has become more important as patients with pain remain on opioids at higher doses for longer periods of time. One setting that highlights the dilemma of OIH is in the opioid-tolerant patient who is hospitalized for painful medical conditions or procedures and is unable to achieve adequate analgesia despite escalating opioid doses. This patient population often requires agents that act synergistically with opioids through different mechanisms to achieve analgesia. Dexmedetomidine is an alpha-2 adrenergic agonist that has been shown to synergize with opioids.

Setting. Tertiary care hospital.

Design. Case series.

Method. Eleven hospitalized patients with OIH received dexmedetomidine to improve pain control and to lower opioid doses while avoiding opioid withdrawal.

Results. A total of 64% (7/11) had substantial reductions in their baseline opioid doses at the time of discharge.

Conclusions. The cases presented provide support for the clinical utility of alpha-2 agonists during opioid dose reduction in patients with OIH as well suggesting that they may contribute to the recovery of normal nociceptive and antinociceptive responses.

Key Words. Opioid-Induced Hyperalgesia; Dexmedetomidine; Alpha-2 Adrenergic Agonists; Opioid Withdrawal; Opioid Tolerance

Introduction

Our understanding of the actions of opioids now encompasses pronociceptive as well as antinociceptive mechanisms. Opioid-induced hyperalgesia (OIH) is characterized by a paradoxical increase in pain intensity, distribution, or sensitivity caused by prolonged or escalating doses of opioids [1]. Currently, there are no epidemiologic studies of incidence and prevalence of OIH [2]. As awareness of OIH is heightened, human studies are being performed to better understand this phenomenon. To date, studies suggest the development of OIH in people with opioid dependency on methadone maintenance therapy, perioperative exposure to opioids in patients undergoing surgery, and short-term opioid exposure in human volunteers [3–5]. These studies are limited due to their retrospective or cross-sectional design [3,6]. Therefore, they are unable to differentiate between tolerance and OIH nor can they demonstrate a direct cause and effect relationship between opioids and the development of OIH. To add to the confusion, studies with similar designs show conflicting results [1,3]. For example, in a study by Guignard (2000), the administration of relatively large intraoperative doses of remifentanil resulted in acute opioid tolerance, increased postoperative pain and higher opioid requirements [7]. However, Cortinez (2001) performed a similar study using intraoperative remifentanil and found similar morphine consumption and pain scores among the two groups [8]. An evidence-based review by Fishbain (2009) showed that the strongest evidence for OIH in humans comes from normal volunteers receiving opioid infusions [6]. Other reports reviewed did not show sufficient evidence to support or refute OIH in humans. To date, the most promising human study is a prospective study of six chronic low back pain patients who were placed on morphine therapy for a period of 4 weeks. Despite the study's small sample size and lack of placebo group, it does demonstrate the development of OIH in opioid naïve patients placed on moderate doses of opioid therapy using quantitative sensory testing (QST) [4].

While human studies for OIH are limited [2], there is a large body of evidence in animal studies [3–6,9–11]. Precise molecular mechanisms of OIH are still being uncovered. It is thought to result from neuroplastic changes in the peripheral and central nervous systems that lead to sensitization of pronociceptive pathways [1,3,12]. Often difficult to distinguish from opioid tolerance, treatment of OIH

is complex due to lack of clear diagnostic criteria, the compelling need to provide analgesia with limited alternative options, and risk of opioid withdrawal with opioid reduction.

One setting that highlights the dilemma of OIH is in the opioid-tolerant patient who is hospitalized for painful medical conditions or procedures and is unable to achieve adequate analgesia despite escalating opioid doses. Many hospitalized patients experience pain related to the treatment of conditions that may result in iatrogenic pain. Organ transplants, immunosuppression, and complex surgery all can result in persistent pain states that are difficult to treat and that usually require opioid analgesics. These patients require an increase in their opioid analgesics to accommodate for pain associated with surgical injury [13–15]. We are challenged by cases that no longer respond to aggressive titration of opioid analgesics and who get insufficient pain control with multiple adjuvant analgesics such as anticonvulsants, antidepressants, anti-inflammatory agents, or N-methyl-D-aspartate (NMDA) receptor blockers. Some of these patients cannot be treated with regional analgesic techniques or do not respond to them. A subset of these patients may be diagnosed with OIH when worsening pain, out of proportion to disease progression, accompanies opioid dose escalation.

In some cases, pain becomes intractable to opioids at any dose and goes beyond simple tolerance. These patients may experience pain that is more widespread than their injury and they may become sensitized to stimuli at lower thresholds. This patient population often requires agents that act synergistically with opioids through different mechanisms to achieve analgesia. Such agents may also allow for opioid dose reduction and a return to a normal response to pain therapies. The inpatient pain management consult service at the University of Minnesota Medical Center (UMMC) is utilizing dexmedetomidine (Dex) in the management of OIH in hospitalized patients with intractable pain that is no longer responsive to additional opioid analgesia. The goals of treatment with Dex would be to substantially reduce high opioid doses quickly and improve pain control while preventing opioid withdrawal symptoms.

Dex, an alpha-2 adrenergic receptor agonist, was approved by the US Food and Drug Administration in 1999 for short-term sedation for patients undergoing mechanical ventilation in the intensive care setting [16]. Dex has the advantage of not causing respiratory depression and at anxiolytic doses, it typically does not impair conscious awareness thus allowing for an "interactive sedation" [17,18]. Other clinical settings with reported benefit of Dex include its use for analgesia [19], opioid-sparing effect [20,21], and opioid and benzodiazepine withdrawal [22–25]. As a class, the alpha-2 adrenergic receptor agonists have been shown to produce significant synergy with opioids in mice [26–28]. In these studies, combining an alpha-2 adrenergic receptor agonist with an opioid can increase analgesic potency by an order of magnitude. Such synergy may offer an opportunity to reduce opioid requirements without sacrificing analgesia and thus, effectively "reboot" the analgesic and pain modulating systems.

We set out to use Dex's theoretical synergy with opioids in patients suspected of having OIH to allow us to safely and effectively reduce opioid doses, thereby reducing OIH and improving pain control.

Methods

From 2003 to 2008, the inpatient pain consultation service of the UMMC identified 11 cases presumed to have OIH based on an expedient algorithm that is not validated, which attempts to separate OIH from withdrawal and tolerance or other conditions that share the common feature of lack of responsiveness to opioid analgesia (See Table 1 and Figure 1). These cases were recommended for a trial of Dex. As there is no gold standard for the diagnosis of OIH, the algorithm depicted in Figure 1 represents an empirical approach that identifies other causes of failed pain control despite increasing opioid doses. The Dex protocol requires remaining on or transfer to an intensive care unit for monitoring. A starting dose of 0.2 μg/kg/h of Dex was infused and titrated to control of pain and symptoms of withdrawal. Adverse effects such as bradycardia and hypotension limited the titration. Doses could range from 0.2–0.7 μg/kg/h. The duration of infusion was empirically determined based on the patient's clinical response and stability of their response. Scheduled opioids were reduced by 50–100%, but rescue opioid was available for analgesia when needed. We retrospectively calculated

Table 1 Characteristics that distinguish opioid-induced hyperalgesia (OIH) from opioid tolerance and opioid withdrawal

	Tolerance	Withdrawal	OIH*
Increasing opioid helps	Yes	Yes	No
Pain sensitivity	Same	Increased	Increased
Pain distribution	Same	Same or increased	Increased
Opioid doses	Stable	Reduced	Stable or increased

* Hyperalgesia may occur in the setting of opioid withdrawal, and OIH has been described in the setting of single doses of opioid and in withdrawal states, but this table refers to OIH in the setting of continued or escalating opioid doses.

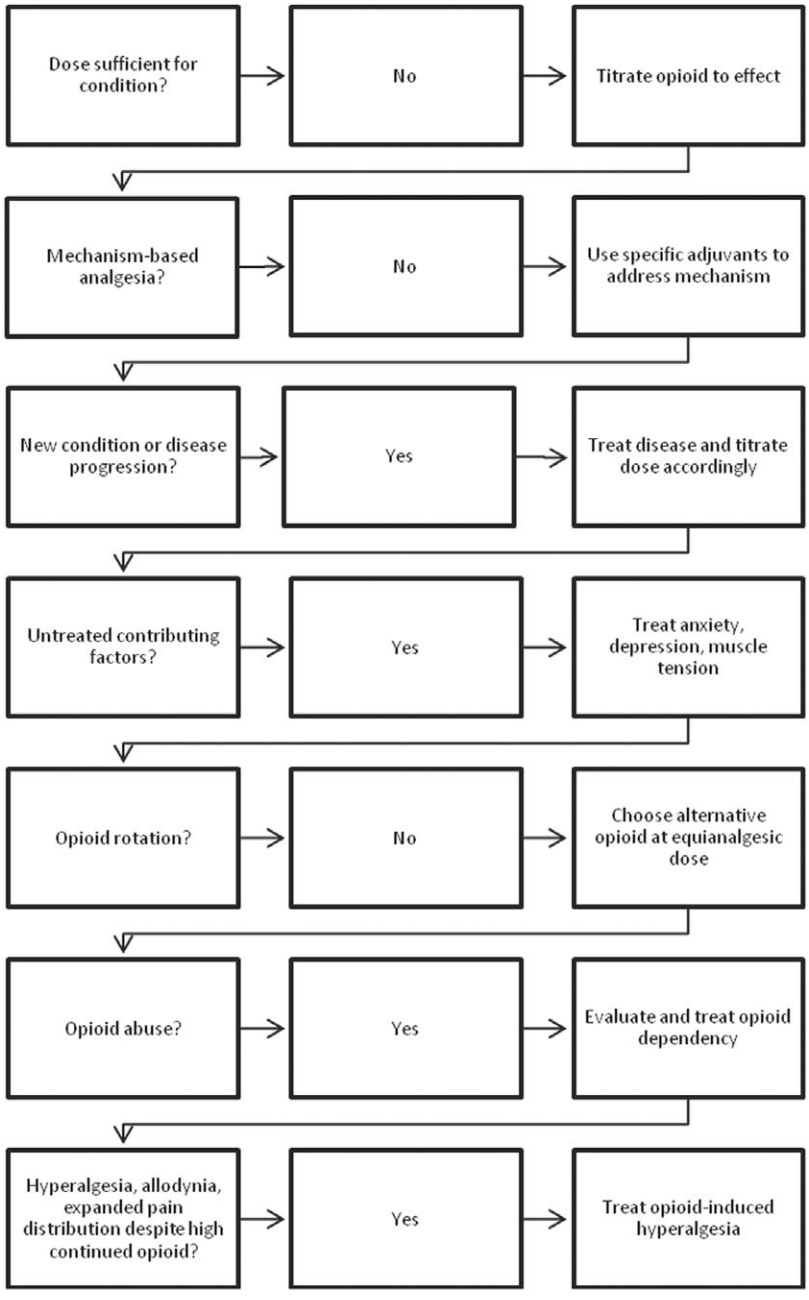
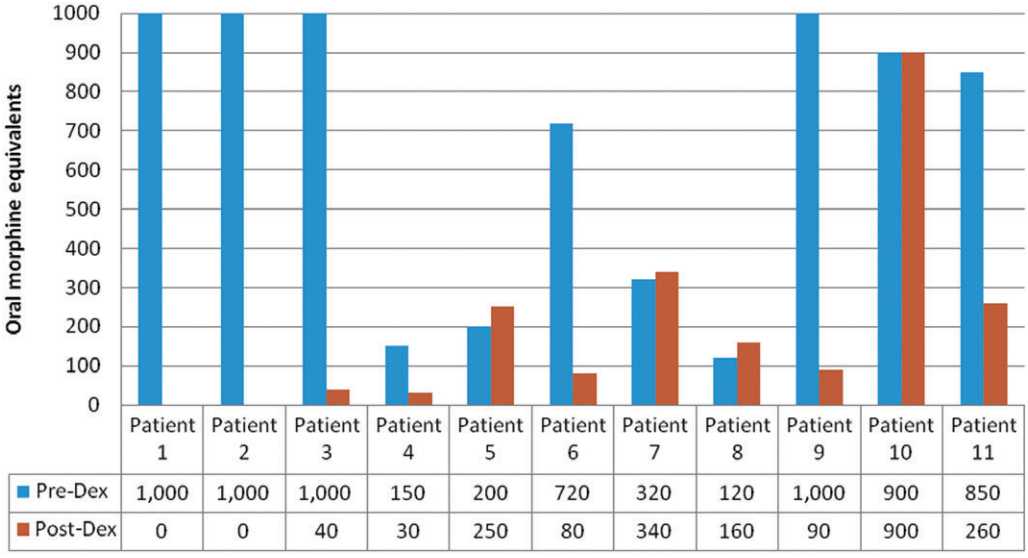


Figure 1 Algorithm for identifying patients with OIH and distinguishing OIH from other causes of failed opioid analgesia. The diagram is composed of a checklist of basic principles of pain assessment and management for acute pain including adequate dosing for the condition, use of mechanism-based pain treatments and medications, attention to the progression of the underlying disease as a source of escalating pain, identifying and managing non-pain sources of distress that may amplify the pain experience, trial of alternative opioid to account for genetically determined individual response differences to a given opioid, and identifying chemical dependency and abuse that may confound proper pain assessment and management. When these basic principles are attended to, increasing pain despite continued or increasing opioids and an expanded pain sensitivity (hyperalgesia) or distribution, OIH may be clinically suspected because other causes of failed opioid therapy have been addressed.



	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Pre-Dex	1,000	1,000	1,000	150	200	720	320	120	1,000	900	850
Post-Dex	0	0	40	30	250	80	340	160	90	900	260

Figure 2 Twenty-four-hour oral morphine equivalents (OME) before dexmedetomidine (Dex) and upon discharge. Doses >1,000 mg OME are set as 1,000 mg.

opioid use in the 24hours preceding Dex treatment and also calculated the scheduled opioid doses upon discharge (Figure 2). Among the patients recommended for Dex, 10 patients did not enter the Dex protocol for various reasons. There were barriers to intensive care unit transfer. Some were started on Dex, but the protocol was not followed. Some patients were excluded due to hypotension. Other patients did not enter the protocol due to the primary service not following pain service recommendations. This case review was approved by the University of Minnesota's institutional review board (Table 2).

Case 1 (Patient No. 11)

A 16-year-old male with a history of pre-B cell acute lymphocytic leukemia and hemophagocytic lymphohistiocytosis had a bone marrow transplant 10 months prior to pain service consultation. Other significant

Table 2 Clinical characteristics of 11 cases of OIH treated with dexmedetomidine (Dex)

Patient number	Age/ gender	Diagnosis	Pain type	Non-Opioids	Opioids	Dex no. of days
1	14/M	BMT ARDS	G-tube	Lorazepam	Methadone Hydromorphone	5
2	9/M	ALL Hemorrhagic cystitis	Widespread	Midazolam	Hydromorphone	7
3	26/F	Pancreatitis/pancreatectomy	Abdominal		Hyrdomorphone	3
4	31/F	Cystic fibrosis Thrombosus	Chest		Hydromorphone	3
5	34/F	Avascular necrosis Morquio synd	Back Joint		Fentanyl	3
6	35/M	Hemophilia A	Joint		Methadone	4
7	49/F	Postoperative Methadone maintenance	Shoulder		Methadone Fentanyl	2
8	35/F	Cystic Fibrosis Lung transplant	Post-op		Fentanyl Oxycodone	3
9	21/M	Pancreatectomy	Abdominal		Fentanyl	2
10	33/M	Hemophilia A Hepatitis C	Joint post-op	Modafinil	Methadone Hyromorphone	4
11	16/M	ALL BMT	Headache Abdominal Graft vs host	Ketamine	Methadone Fentanyl	6

BMT = bone marrow transplant; ARDS = adult respiratory distress syndrome; G-tube = gastrostomy tube; ALL = acute lymphocytic leukemia.

past medical history included invasive aspergillosis, vancomycin-resistant enterococcus, cytomegalovirus (CMV), herpes simples virus (HSV) positive, graft vs host disease, pulmonary hemorrhage, adrenal insufficiency, chronic headaches, hemorrhagic cystitis, and status post-left thoracotomy for a left lingular lobe resection. The pain service was consulted due to the need for perioperative analgesia for a scheduled cholecystectomy. Preoperatively, the patient's pain medications were composed of: methadone 40 mg orally q 6 hours (160 mg daily), fentanyl infusion 600 μg/h, fentanyl boluses 300 μg every 15 minutes as needed (total of 12,600 μg daily), ketamine infusion 10 mg/h, nortriptyline 100 mg daily, and gabapentin 900 mg three times a day (2,700 mg/day). Despite high opioid doses, underlying pain was in poor control.

The pain consult service recommended utilizing Dex postoperatively, stopping fentanyl, using morphine patient-controlled analgesic pump (PCA) 10 mg/h with 5 mg every 10 minutes, and local anesthetic at the surgical site via subcutaneous reservoir. We also recommended discontinuing methadone following surgery and continuing ketamine on an as-needed basis at 20 mg intravenous every 3 hours. Following surgery, Dex was titrated up to 0.7 μg/kg/h, the methadone was continued per the patient's parents' request, and the morphine PCA settings were adjusted to 15 mg/h and 7 mg every 10 minutes as-needed. The patient used three doses of as-needed ketamine over night. On post-op day one, the morphine PCA settings were adjusted to 20 mg/h and 10 mg every 10 minutes and the patient did not need any ketamine. On post-op day two, the patient's pain score was two out of 10 and using morphine PCA at an average of approximately 30 mg/h. The methadone dose was reduced by 50%. On post-op days three through five, the morphine PCA was tapered down due to myoclonus and adequate pain control. The Dex infusion was also tapered down over this time period. Prior to discharge, the patient was able to taper off all methadone and remained only on oral morphine 7.5 mg on an as-needed basis.

Case 2 (Patient No. 6)

A 35-year-old male with a history of hemophilia A with factor VIII inhibitor and hepatitis C has had multiple hemarthroses and was admitted for an acute left ankle bleed. He was taking 400 mg per day of oral methadone and required modafinil to maintain alertness. In the hospital, he was using the same methadone dose plus hydromorphone 20 mg IV every 3 hours to control the acute ankle pain with little relief. His pain management is complicated by sleep apnea and unwillingness to use a positive pressure device, and by myoclonic jerking that was provoking his pain. A Dex infusion was started and continued for 3 days at 0.1–0.2 μg/kg/h. Methadone was reduced to 50 mg orally twice daily and IV hydromorphone was available at 6 mg rescue doses but only utilized twice in 24 hours. The Dex infusion was maintained at 0.1 μg/kg/h because of hypotension. Pain control improved dramatically and he was more alert. At no time were there any opioid withdrawal signs or symptoms noted. The patient expressed dismay at the low doses of opioids in spite of his good pain control and lack of withdrawal symptoms. He stated that he felt "almost like I lost a friend."

Case 3 (Patient No. 9)

A 21-year-old male with acute relapsing and chronic pancreatitis was admitted to undergo a pancreatectomy with islet autotransplantation for chronic abdominal pain. Preoperative pain medication included sustained release oxycodone 20 mg every 12 hours and oxycodone with acetaminophen as needed for additional pain. He underwent a total pancreatectomy, duodenectomy, splenectomy, cholecystectomy, liver biopsy, and intraportal islet autotransplantation and was transferred to the intensive care unit. At the time of pain service consultation, the patient was receiving a fentanyl infusion of 1,100 μg/h that had been titrated up over the past 3 days with little effect on pain. The patient was alert and oriented, tachycardiac and would not allow anyone to examine his abdomen due to severe pain and sensitivity to the lightest palpation. Pain was diffusely distributed over the abdomen. The pain service recommended starting a Dex infusion at 0.2 μg/kg/h titrating up to a maximum of 0.7 μg/kg/h. The fentanyl infusion was changed to morphine using PCA at 10 mg/h and 2 mg every 10 minutes. The next day, pain control was adequate and the patient would allow examination of the abdomen. Dex was discontinued and morphine PCA continued. At the time of discharge, the patient transitioned to oral opioid analgesics at doses less than the preoperative equivalent.

Discussion

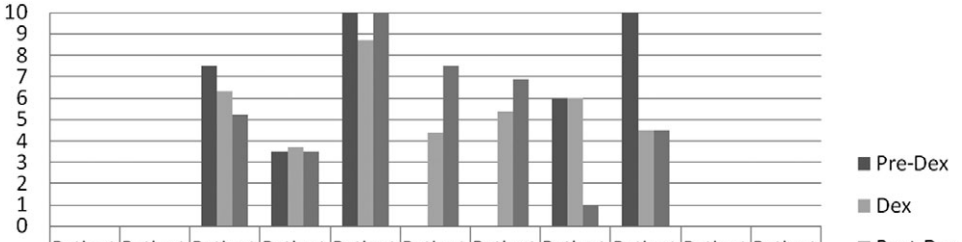
These three cases illustrate many of the features of the 11 cases in our series (Figure 2). All but four of the patients (64%) had substantial reductions in their baseline opioid doses at the time of discharge. Of the patients who did not reduce their opioid doses post-Dex, patient no.5 had musculoskeletal pain due to Morquio mucupolysaccharidosis and multiple orthopedic surgeries. She was admitted with an overdose. She was intubated and Dex protocol-initiated. Nursing notes document improved function, less agitation, and appearance of comfort despite pain scores remaining high. Patient no. 7 was on methadone maintenance for addiction as an outpatient taking 140 mg/day. She was admitted for an orthopedic shoulder surgery. She was on escalating doses of IV fentanyl without analgesia. With Dex, pain control was improved, but she continued her methadone maintenance at the same dose. Patient no. 8 underwent a bilateral single lung transplant for cystic fibrosis. Six days postoperatively, she was on 300 μg/h of IV fentanyl with agitation, and more global pain when Dex was initiated. Pain scores improved while on Dex and afterward from an average of six out of 10 prior to Dex to an average of 1/10 after Dex, even though the opioid dose remained about the same. Patient no. 6 was admitted following arthroscopic knee surgery in the setting of hemophilia. His home methadone regimen was composed of 360 mg/day. Dex was initiated

in order to reduce the home methadone dose at the request of his outpatient pain physician due to presumed OIH. Postoperatively, the methadone dose steadily climbed back toward baseline, and he was found to have a hemorrhage in the operated knee that required reoperation. These four cases of failed opioid reduction include three that were postoperative and three of the four cases were put on fentanyl in the hospital. This raises the question of whether the postoperative state predisposes to OIH. It also suggests that some opioids may be more likely to produce OIH than others [29–31].

None of the patients experienced any significant withdrawal in spite of abrupt opioid reductions and prolonged use of opioids prior to Dex treatment. All of the patients were on daily opioid analgesics of greater than 30 mg of oral morphine equivalent for at least 1 month. Pain control was improved in most of the patients and was at least no worse than pre-Dex pain control in any of them (Figure 3). Even when pain intensity scores remained high, there was often subjective global improvement, and the impression of the treating physicians and nurses was that pain behaviors were less and medical management was easier. There was incomplete pain intensity data recorded. Some patients were intubated and sedated so that numerical pain ratings could not be obtained and behavioral pain assessments could not be compared. For those patients where numerical pain scores were available, the mean pain intensity 24 hours before Dex was 7.4 on the 0–10 numerical rating scale. During Dex infusion, mean pain scores were 5.6, and 24 hours post-Dex, the mean pain scores were 5.5 (Figure 3). One could argue that pain levels in hospitalized patients should return to zero when the acute phase of their illness resolves, but in our series, the disease burden was so high that pain elimination was not possible nor expected. Our case 1 illustrates this well with the multiplicity of medical problems, each concordant with having severe or ongoing pain. One can not be positive that all of the cases in this series had OIH and not some other cause of worsening pain in the face of escalating opioid doses. Case 3 may represent acute postoperative pain that simply did not respond to opioid analgesia. In this case, OIH was suspected due to rapid escalation of opioid analgesics with worsening pain and increased sensitivity to very minimal physical contact. However, without a gold standard diagnostic tool, other explanations for this presentation are plausible.

In this retrospective case series, it is not possible to say if hospital stays were shorter or other outcomes were better. The patients represented a very heterogeneous group—each having complex medical conditions. All of the patients were stuck in a situation of unrelenting pain despite vigorous efforts by the pain service to get pain under control. It was our impression that most of the patients receiving Dex were able to turn the corner and achieve satisfactory pain control in a manner that would not have occurred by staying the course. As treatment with Dex was time-limited, and pain control remained improved in most of the patients with less opioid, Dex appears to have a *rebooting* effect on opioid analgesia in that lower doses of opioid provide better pain control even after Dex is discontinued.

Conclusions drawn from this case series are limited by the small number of patients, lack of a comparison group, and the retrospective nature of this case series, which supports descriptive statistics only. It is also limited by the lack of a gold standard diagnostic tool or even an accepted set of clinical defining criteria for the diagnosis of OIH[32]. The algorithm we used (Figure 1) is an empirical tool for identifying OIH by a process of elimination. It is composed of a checklist of reasons why opioids may fail to provide pain control followed by a treatment plan to address those causes of opioid failure. Such an algorithm is inherently



	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Pre-Dex			7.5	3.5	10			6	10		
Dex			6.3	3.7	8.7	4.4	5.4	6	4.5		
Post-Dex			5.2	3.5	10	7.5	6.9	1	4.5		

Figure 3 Average Numerical Pain Rating during the period 24 hours pre-dexmedetomidine (Dex) infusion, during Dex infusion, and 24 hours post-Dex infusion. For some patients, data were not available, not recorded, or patient pain intensity was based on other scales for intubated or sedated patients (cells left blank).

limited by lack of physiologic data driving the decision-making process and the diagnosis. Future studies might validate this algorithm in a prospective manner with a comparison group that is treated with continued opioid titration. QST shows promise as a means of directly measuring hyperalgesia and tracking changes over time in an objective way that serves as a reliable diagnostic tool for OIH.

Dex appears to be able to "reboot" opioid sensitivity in patients who have developed OIH or opioid tolerance. To date, no studies report the use of Dex specifically for the treatment of OIH. This case series supports the value of further work to clarify the mechanisms of synergy of the alpha-2 adrenoreceptor agonists with opioids and the role of this class of drugs in the management of OIH.

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