

Editorial



Spinal Morphine-Induced Hypothermia Syndrome: A **Closer Look**

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Editorial

While neuraxial opioids for post-op pain control came into common use in the early 1980s, it was not until a decade later, in 1992, when the first case report¹ was published about an unusual side effect of the spinal morphine. It was a hypothermia that was not only *profound* [≤34°C], but *refractory* to usual rewarming methods, and delayed in onset [about 2.5 to 3 hours from initial dose] and resolved in 6-8 hours after onset. It also was associated with paradoxical signs and symptoms such as subjective hyperthermia or euthermia while hypothermic, and concurrent shivering and diaphoresis. Subsequent case reports²⁻¹¹ over the next three decades revealed an interesting subset of patients who have psychological symptoms as well - anxiety, dysphoria, out-of-body experiences, weightlessness, and visual disturbances. What have we learned about this syndrome in the last 30 years or even last 3 years? This editorial will take a closer look at how this syndrome has evolved.

This first case report is remarkable in that it involved a male patient undergoing skin grafting as all subsequent case reports involved female patients having C-sections except for one female undergoing total knee arthroplasty.⁴ All cases involved a spinal anesthetic except one which utilized a combined spinal-epidural (CSE) technique, and in this case,⁵ the morphine was given epidurally, and the sufentanil was given spinally. Other case reports show sufentanil being used with morphine about 25% of the time and fentanyl being used with morphine about 50% of the time. Because morphine is present in all the cases, almost all attempts to name this syndrome include morphine as does the name this author chose - spinal morphine-induced hypothermia syndrome [SMHS]. It has also been termed neuraxial morphine syndrome, Duramorph® spinal hypothermia, and malignant hypothermia syndrome. The last handle is probably inappropriate as no patient has ever died from this syndrome, and it resolves on its own after a few hours. Does the dose of intrathecal morphine make a difference whether a patient will get SMHS? Previous case reports show a wide range of dosages, from 0.10mg up to 0.5mg. so it is doubtful the dose is important, but then these are all anecdotal reports and not randomized controlled studies. Again, the many cases implicate the added sufentanil or fentanyl added to the local anesthetic as a determinant, not just the morphine. The morphine dosage, however, does seem to be important as to how long the regular hypothermia with intrathecal morphine lasts: the higher the dose, the longer the hypothermia.¹¹

So, are males naturally resistant to SMHS since there is only one case report involving a male patient ever? The putative mechanism of this syndrome is activation of δ -opioid receptors in the dorsomedial hypothalamus, which "turns off" the cold input to the brain. The κ receptor and GABA receptor may also play a role here but is less well understood.^{3-6,11} However, there are several factors to consider: first, the average male is 12.5cm taller than the average



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female. Since SMHS involves morphine reaching the hypothalamus, additional height would be a protective effect against SMHS. Second, there are other factors that increase cephalad spread including increasing age, shorter stature, female gender, decreased CSF density, reduction in CSF volume, and progesterone increasing neuronal sensitivity.¹¹⁻¹³ The last three are particularly related to pregnancy. Third, many patients who have a spinal anesthetic for C-section do not receive any kind of benzodiazepine sedation, whereas patients who receive morphine spinals for total joints or other non-obstetric surgery do. Could these benzodiazepines prevent SMHS from occurring in the first place in non-obstetric cases?

Does the previously noted relationship¹⁰ between short stature and advanced age in morphine-induced hypothermia apply to SMHS as well? Here is what the newer case reports show: Berstein¹⁴ described a case of a female patient undergoing c-section who was 50 years old and 163 cm tall who developed SMHS and was successfully treated with nalbuphine. DeLeon¹⁵ also described a patient who was 42y/o and 157cm tall for C-section who developed SMHS but was successfully treated with 1mg midazolam IV. Munday¹⁶ described three patients with SMHS with heights of 163, 162, and 168cm. One patient was 35y/o but two had no recorded age. Wolla¹⁷ had a patient with SMHS who was 30y/o but height was not recorded. By private correspondence, a doctor self-reported personally having had SMHS, and her age was 33, and her height was a towering 175cm. This additional information strengthens the idea that increasing age increases the chance of having SMHS, but not necessarily short stature, as two of the six patients were over the median height of a woman. These recent case reports do indicate two new treatments for SMHS: midazolam, 1mg. IV, which is more readily available than lorazepam, and nalbuphine, 2.5 to 5mg. IV, which treats the SMHS but does not reverse the analgesia of the spinal morphine.

Two questions remain: What is the true incidence of SMHS and is SMHS a unique syndrome or just the far end of the morphine-induced hypothermia continuum? Unfortunately, there are no randomized prospective controlled trials for SMHS, which is not surprising in such a rare phenomenon. But how rare is it? Looking at the only author that has published a prospective controlled study related to SMHS, Hess¹¹ divided his patients into 3 groups: normothermic, hypothermic and hypothermic with symptoms. They give an incidence of 7/100 or 7% for the symptomatic group, which one would assume to be SMHS. However, none of the patients met all the criteria of SMHS: profound hypothermia $\leq 34^{\circ}$ C, delayed onset of hypothermia and refractoriness to common warming methods. The symptomatic patients did have some paradoxical signs and symptoms and IV lorazepam brought this group rapid relief.

Maybe it is time to look at Hess' study a little more closely. All his patients were above the average maternal age (28y/o), and almost half met the criterion for advanced maternal age (35y/o). His definition of hypothermia is the standard definition of hypothermia, \leq 35.8°C, not the definition of profound hypothermia, \leq 34°C. The symptomatic hypothermia group was 2cm shorter than the normothermic and asymptomatic patients. Hess used 0.25mg Duramorph and 25µg of fentanyl in the spinal. OR temperature was kept at 35°C and IV fluids were warmed to 42°C. Could the preemptive warming have kept these patients from getting the full-blown SMHS? Or could the fentanyl in the spinal have caused a milder form of SMHS. Was his patient population more predisposed to hypothermia, or less predisposed? Were any of the symptomatic hypothermic patients truly SMHS patients? Perhaps one or possibly two met the definition of profound hypothermia. This again begs the question - is SMHS a separate distinct entity or is it part of the continuum of morphine-induced hypothermia?

An informal survey of current and past hospital affiliations showed an incidence of 0-7/10,000, established by estimation. A survey via private correspondence revealed an incidence of 1.3/10,000. Recently-trained colleagues deny ever having heard about it and never exposed to SMHS in their residency training programs even though, with the first case reported in 1992, virtually everyone in practice today should be up on it. Could SMHS patients been overlooked in a less-aggressive temperature-seeking nursing unit? It is possible that a post-C-section patient who came to the floor around 10PM may have been allowed to sleep and never had a subnormal temperature detected; however, it seems unlikely that this could explain the 100-fold discrepancy (7/10,000 vs. 7/100). In our series of two patients, they caused a major disruption at our hospital, involving even the chief nursing officer.

Summary

Over the past thirty years, midazolam and nalbuphine have come across as better treatments for SMHS, but many facets of this interesting syndrome remain an enigma. It has evolved from a syndrome affecting a male patient undergoing skin grafting to a syndrome involving only female patients undergoing a C-section. Although SMHS seems to be a well-defined entity, there are several cases depicting milder forms of SMHS, which are not as striking but have some of the same paradoxical signs and symptoms as SMHS. These milder cases and the rarity of SMHS make it difficult to establish whether it is truly a unique syndrome and/or what the true incidence really is. More research could be directed at this topic, but with such a rare syndrome, it would be almost impossible to perform prospective randomized controlled trials to uncover the truth.

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Conflicts of Interest

The author declares that there are no conflicts of interest.

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