Separation Anxiety as a Mediator Between Acute Morphine Administration and PTSD Symptoms in Injured Children

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ABSTRACT: Emerging evidence suggests that individuals who receive morphine while hospitalized demonstrate a decrease in symptoms of posttraumatic stress disorder (PTSD). However, the mechanisms of effects are not yet well understood. The goal of the current study was to examine three possible mediators for this effect. Sixty-one injured (burns, motor vehicle accidents, falls, and assaults) children were assessed during hospitalization and again 3 months post discharge. Assessment included acute and follow-up child report measures of pain, PTSD, and anxiety symptoms, as well as a medical record review for medication administration and pulse during hospitalization. Pathway analyses were conducted to test the potential mediating roles of pain reduction, noradrenergic attenuation, and separation anxiety on the association between morphine and PTSD. Results suggest that a reduction in separation anxiety may mediate the association between morphine administration and PTSD symptom reduction at 3 months. These findings have implications for our understanding of morphine's effects on psychological functioning following an acute injury and for direct clinical care.

KEYWORDS: posttraumatic stress disorder; morphine; separation anxiety; children; injuries

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INTRODUCTION

The Center for Disease Control and Prevention (CDC) reported that 8.3 million children and adolescents under the age of 15 years were seen in hospital emergency rooms for injuries in 2003.[1] Posttraumatic stress disorder (PTSD) is reportedly one of the most prevalent psychiatric problems in children who have experienced injuries.[2] In a small sample ($n = 24$) of hospitalized burn-injured children, Saxe and colleagues have reported a significant inverse relationship between morphine dose the child received in the hospital and his or her change in PTSD symptoms over the course of 6 months after discharge.[3] This finding was recently replicated in a larger sample of burn and nonburn injured children ($n = 61$).[4] The present study uses this cohort of injured children to investigate three possible mechanisms relating morphine to reduction in posttraumatic stress symptoms: pain, norepinephrine (assessed via heart rate), and separation anxiety. We chose these possible mechanisms for a variety of reasons. First, pain is related to PTSD[3] and opiate drugs are clearly related to pain reduction; therefore, acute treatment with morphine may reduce PTSD symptoms by diminishing acute pain. Second, an emerging literature has indicated that higher heart rates in the acute trauma setting are associated with an increased risk for developing PTSD.[5] The most likely mechanism of this association is the norepinepherine system that is integrally involved in the consolidation of emotional memory.[6] Morphine clearly attenuates noradrenergic activity in the brain,[7,8] therefore, a decrease in norepinepherine caused by morphine dose may lead to a decrease in PTSD symptoms. Last, past research has found that a decrease in separation anxiety is directly related to a decrease in PTSD symptoms.[9] Animal research findings further suggest that both endogenous and exogenous opioids are linked to the attachment/affiliative motivational system in the brain.[10] Specifically, morphine has been found to decrease separation distress in rat pups.[11] This relationship suggests that a decrease in separation anxiety may act as a mediating factor between morphine dose and posttraumatic stress symptoms. On the basis of the past evidence, we hypothesized that the three aforementioned variables may act as mediating factors between morphine dose and PTSD at 3 months.

METHODS

Sixty-one physically injured children were included in this study (41 male; mean age 12.15 years, SD = 3.41, range 6–18). Of these, 24 children had been admitted to the Shriners Burns Hospital in Boston with acute burns, and 37 were admitted to the Boston Medical Center with acute injuries, including motor vehicle accidents (67.5%), falls (21.6%), and assaults (10.8%). The average length of stay was 9.02 days (SD = 9.01, range 1–48).

Both groups of participants were assessed while in the hospital and again 3 months post discharge. All injured children admitted to the hospital were eligible for the study unless they or their guardians were unable to speak English well enough to complete the assessment or they had been mechanically ventilated during their hospitalization. This final exclusion was on the basis of the fact that mechanically ventilated patients tend to receive much higher doses of opiates than other patients on account of less concern regarding respiratory compromise.

A research associate interviewed participants after their physician had deemed them medically stable. Clinical assessment included the Child PTSD Reaction Index, Multidimensional Anxiety Scale for Children (MASC), and the Colored Analogue Pain Scale. During hospitalization, the medical records of each participant were reviewed for medication administration data and pulse. Each opiate administered over the course of the child's stay was summed and divided by the child's weight and the length of their hospitalization (days) to derive a mg/kg/day dose for each medication. In order to standardize all opiates administered, an equivalency dose of oral morphine was calculated using a conversion protocol from a pharmacology textbook.[12] A mean pulse was calculated by dividing the sum by the number of observations of pulse recorded by the child's nurse during his or her hospitalization.

Arrangements were made for all participants to return to either the Shriners Burns Hospital or the Boston Medical Center for a 3-month follow-up interview, which again included the Child PTSD Reaction Index, MASC, and the Colored Analogue Pain Scale.

RESULTS

Three possible variables mediating the association between morphine and PTSD symptom reduction were investigated in this study: pain reduction, norepinephrine attenuation (assessed via heart rate), and separation anxiety. Results revealed that pain was not significantly correlated to either morphine ($r = -0.060$, $P = 0.662$) or PTSD at 3 months ($r = 0.149$, $P = 0.284$). Heart rate was significantly correlated to morphine ($r = 0.357$, $P = 0.006$), but not to PTSD at 3 months ($r = 0.094$, $P = 0.485$). A significant negative correlation was found between separation anxiety and morphine ($r = -0.374$, $P = 0.021$), and a trend between separation anxiety and PTSD at 3 months was found ($r = 0.292$, $P = 0.075$). A path analysis including morphine, separation anxiety, and PTSD at 3 months was conducted using Mplus.[13] Results indicated a significant negative relationship between morphine and separation anxiety (ß = −0.335) and a significant positive relationship between separation anxiety and PTSD at 3 months (ß = 0.314). This pathway showed strong fit indices [chi-square = 0.883; Comparative Fit Index (CFI) = 1; Tucker

Lewis Index (TLI) = 1.466; and Root Mean Square Error of Approximation (RMSEA) = 0.00].

DISCUSSION

Recent studies have demonstrated an association between administration of morphine following a traumatic injury and reduction in PTSD symptoms. However, the mechanisms for this effect are not understood. The goal of this study was to examine three possible mechanisms suggested by various literatures: reduction in pain, attenuation of noradrenergic activity, and decrease in separation anxiety. The major findings of this study suggest that separation anxiety may be an important mediator in the relationship between morphine and PTSD symptom reduction. That is, the use of morphine during acute hospitalization appears to lead to a decrease in the child's separation anxiety, and this decrease is associated with a decrease in the child's PTSD symptoms 3 months post injury. These results connect the findings of previous work demonstrating that opioids result in attenuation of the reaction to social separation[10] and children's levels of acute separation anxiety are related to PTSD symptom severity.[9] The current analyses did not provide support for the roles of pain reduction or attenuation of noradrenergic activity in the pathway from morphine to PTSD symptom reduction. In sum, the results of the present study provide support for a model-linking morphine administration, separation anxiety, and PTSD symptomatology. On the basis of these results, future research using experimental designs should be pursued in an attempt to gain a more complete understanding of morphine's effects on PTSD and shape clinical care.

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REFERENCES

1. McCaig, L.F. & C.W. Burt. 2005. National hospital ambulatory medical care survey: 2003 emergency department summary. Vital and Health, Statistics: **358**.
2. Stoddard, F.J. & G. Saxe. 2001. Ten-year research review of physical injuries. J. Am. Acad. Child Adolesc. Psychiatry **40:** 1128–1145.
3. Saxe, G. *et al*. 2001. Relationship between acute morphine and the course of PTSD in children with burns. J. Am. Acad. Child Adolesc. Psychiatry. **40:** 915–921.
4. Saxe, G. & K.C. Koenen. 2006. Acute morphine administration and the course of PTSD symptoms in medically hospitalized children. N. Engl. J. Med. Submitted.
5. Shalev, A.Y. *et al*. 1998. A perspective study of heart rate response following trauma and the subsequent development of posttraumatic, stress disorder. Arch. Gen. Psychiatry **55:** 553–559.

6. PITMAN, R.K. 1989. Post-traumatic, stress disorder, hormones, and memory [editorial]. Biol. Psychiatry **26**:221–223.
7. ASTON-JONES, G. *et al*. 1993. Opiates influence locus coeruleus neurons by potent indirect and direct actions. *In* Neurobiology of Opiates. R.P. Hamner, Ed.: 175–221. CRC. Boca Raton, FL.
8. CHRISTIE, M.J. 1991. Mechanisms of opioid actions on neurons of the locus coeruleus. Prog. Brain Res. **88:** 197–205.
9. SAXE, G. *et al*. 2005. Pathways to PTSD, part 1: children with burns. Am. J. Psychiatry **162:** 1299–1304.
10. NELSON, E.E. & J. PANKSEPP. 1998. Brain substrates of infant- mother attachment: contributions of opioids, oxytocin, and norepinephrine. Neurosci. Biobehav. Rev. **22:** 437–452.
11. PANKSEPP, J, J.D. NEWMAN & T.R. INSEL. 1992. Critical conceptual issues in the analysis of separation distress systems of the brain. *In* International Review of Studies on Emotion, vol. 2. K.T. Strongman, Ed.: 52–72. John Wiley & Sons. Chichester, UK.
12. REISINE, T & G. PASTERNAK. 1996. Opioid analgesics and antagonists. *In* The Pharmacological Basis of Therapeutics. J.G. Hardman, Ed.: 521–556. McGraw Hill Publishing Co. New York.
13. MUTHEN, L.K. & B.O. MUTHEN. 1998. Mplus, User's Guide. Muthen & Muthen. Los Angeles, CA.