Published in final edited form as:

Paediatr Anaesth. 2017 March ; 27(3): 290–299. doi:10.1111/pan.13066.

A case-controlled comparison of postoperative analgesic dosing between girls with Rett syndrome and girls with and without developmental disability undergoing spinal fusion surgery

Chantel C. Barney¹, Alyssa A. Merbler², Kelsey Quest², Breanne J. Byiers², George L. Wilcox³, Scott Schwantes¹, Samuel A. Roiko¹, Timothy Feyma⁴, Arthur Beisang⁴, and Frank J. Symons²

¹Gillette Children's Specialty Healthcare, St. Paul, USA

²Department of Educational Psychology, University of Minnesota, Minneapolis, USA

³Department of Neuroscience, Pharmacology and Dermatology, University of Minnesota Medical School, Minneapolis, USA

⁴Rett Syndrome Clinic, Gillette Children's Specialty Healthcare, St. Paul, USA

Abstract

Background—Rett syndrome (RTT) is associated with severe motor and communicative impairment making optimal postoperative pain management a challenge. There are case-reports documenting reduced postoperative analgesic requirement in RTT.

Aim—The goal of this preliminary investigation was to compare postoperative analgesic management among a sample of girls with RTT compared to girls with and without developmental disability undergoing spinal fusion surgery.

Method—The medical records of 8 girls with Rett syndrome (mean age=13.2 years, SD=1.9), 8 girls with developmental disability (cerebral palsy [CP]; mean age= 13.1 years, SD= 2.0), and 8 girls without developmental disability (adolescent idiopathic scoliosis [AIS]; mean age=13.4, SD=1.8) were reviewed. Data related to demographics, medications, and route of drug administration were recorded.

Results—Girls with RTT received significantly fewer morphine equivalent opioids postoperatively ($M = 0.26$ mg/kg/day, $SD = 0.10$) compared to girls with AIS ($M = 0.47$ mg/kg/day, $SD = 0.13$; 95% CI -0.34 to -0.08 ; $p = .001$) and girls with CP ($M = 0.40$ mg/kg/day, $SD = 0.14$; 95% CI -0.27 to -0.02 ; $p = .01$). Girls with RTT received significantly fewer opioid patient controlled analgesic (PCA) bolus doses (given by proxy; $M = 42.63$, $SD = 17.84$) compared to girls with AIS ($M = 98.25$, $SD = 52.77$; 95% CI -96.42 to -14.83 ; $p = .01$). There was also some evidence indicating girls with RTT received fewer bolus doses compared to girls with CP ($M = 80.88$, $SD = 38.93$; 95% CI -79.05 to 2.55 ; $p = .06$). On average, girls with RTT also received smaller total doses of acetaminophen, diazepam and hydroxyzine.

Conclusion—This study highlights possible discrepancies in postoperative pain management specific to girls with RTT and suggests further investigation is warranted to determine best practice for postoperative analgesic management for this vulnerable patient population.

Keywords

opioid; pain; scoliosis; communication disorders; adolescent; pediatric

Rett syndrome (RTT) is a rare genetic disorder with an estimated incidence of 1 in 10,000. RTT almost exclusively affects females and is caused by mutations in the methyl-CpG-binding protein 2 gene (*MECP2*). The disease is characterized by the progressive loss of previously acquired developmental milestones typically between the age of 6 to 18 months followed by the development of stereotypical hand movements, severe impairments in language, and gait apraxia. The majority of girls and women with RTT also have epilepsy, autonomic and respiratory concerns (e.g., breath holding, increased risk for pneumonia), gastroesophageal reflux, constipation and associated gastrointestinal issues, and scoliosis.^{1,2}

Despite the myriad health conditions experienced by girls with RTT, some likely to be associated with pain, pain insensitivity remains part of the diagnostic criteria. The initial scientific evidence for pain insensitivity was derived from several case study reports. Early case studies highlighted the lack of response/reactivity in girls with RTT during accidental injuries (e.g., falls, exposure to fire).³ In a more recent large survey study (N=646) the majority of parents responding to a single item reported reduced pain sensitivity in their daughters (although, some did report increased sensitivity).⁴ This study by Down and colleagues (2010) also provided preliminary evidence that genotype may play a role in pain sensitivity, as a C-terminal, p.R168X or p.R306C mutation was associated with decreased pain sensitivity.

In a subsequent survey study, in which parents were asked more specific questions about their daughter's pain based on items from a validated non-verbal pain scale, the majority reported that their daughters experienced a great deal of chronic pain. Almost a quarter of the sample (24%; out of 44) reported that their daughters experienced pain for more than 7 days in the previous month.⁵ The frequency of pain episodes significantly correlated with the number of pain sources and the number of chronic health conditions.⁵ In a further investigation examining the relation between parent report (proxy report of pain symptoms) and directly observed pain behaviors (pain signs) during a physical exam-based procedure, Barney et al.⁶ found the majority of parents (89%) reported their daughter had experienced pain in the previous week. The most common etiologies of chronic pain included gastrointestinal, musculoskeletal, and seizure related pain. On average, the pain reported was intense (rated 6 out of 10) and long in duration (lasting up 25 hours in the previous week). Parents reported a broad array of modalities through which their daughters expressed pain (e.g., facial expressions, vocalization). Pain expression also appeared intact and frequent when coded observationally during a physical exam consistent with behavioral pain expression in other non-verbal populations with severe neurodevelopmental disabilities.⁶

The detailed subjective reports of pain experience and objective coding of pain expression during physical exam in girls with RTT suggests the issue surrounding pain in RTT may be a

detection issue rather than a sensitivity issue.^{5,6} Severe motor and communicative impairments limit the ability of girls and women with RTT to communicate their pain experiences in conventional ways (i.e., self-report). Because of this, there is the possibility that pain may be overlooked and undertreated in RTT. This possibility is further supported by the finding that despite concerns about health, almost half (43%) of parents reported they were unsure how to tell reliably when their daughter was in pain.⁵

Given the general health issues associated with the syndrome and the ambiguity (and difficulty) in detecting pain expression, optimizing medical care in general and pain management in particular remains a challenge. Painful surgical procedures are likely to occur for girls and women with RTT. Scoliosis is present in 50% of girls with RTT frequently leading to spinal fusion, tonsillectomies are performed to treat obstructive sleep apnea, and gastrostomy tube placement is often required to resolve feeding issues.⁷⁻⁹ Considering the complexities of pain assessment in girls with RTT and the diagnostic criteria indicating pain insensitivity, there seems reason to be concerned about how pain is managed in the postoperative period. In a previous study investigating postoperative pain management following spinal fusion surgery for children with and without cognitive impairment, children with cognitive impairments received significantly less total opioids and were less likely to have their pain assessed consistently.¹⁰ Specific to RTT, there have been case reports documenting reduced postoperative analgesic requirements and increased sensitivity to sedatives in RTT following surgical intervention.¹¹⁻¹³ The case studies included behavioral ratings and maternal report and suggested reduced pain (expression). Other case reports document reduced use of sedatives during painful procedures for girls with RTT based, in part, on prior claims regarding reduced analgesic requirement in the RTT population.¹⁴ A recent retrospective review of 24 girls with RTT undergoing 29 surgical procedures did not confirm the case-study reports of reduced analgesic requirements following surgery. Although a control group was not included, the type and dosing of opioids delivered did not differ from standard practice for pediatric populations.² Additionally, when 8 girls with RTT were compared to large samples of girls with idiopathic scoliosis and girls with neurologic scoliosis, Rumbak et al¹⁵ found that girls with RTT actually received significantly more morphine equivalent opioids postoperatively compared to the typically developing girls with idiopathic scoliosis.

The purpose of the current study was to further compare postoperative pain assessment scores and management practices in girls with RTT and extend the Karmaniolou et al² study by comparing a RTT sample against age and gender matched controls across the same surgical procedure. Because previous studies have shown a discrepancy in pain management based on cognitive impairment associated with developmental delay¹⁰ two comparison groups were included in this study. One comparison group included typically developing adolescent females with adolescent idiopathic scoliosis (AIS) and the other group included female adolescents with cerebral palsy (CP) with severe motor and communicative impairments. The aim of this study was to compare the total opioid doses for girls with RTT compared to girls with AIS (no motor or cognitive impairments) and girls with CP (severe motor and cognitive impairments comparable to RTT) all of whom underwent spinal fusion surgery.

Methods

Following institutional review board approval, all 12 children with Rett Syndrome who had undergone spine fusion surgery at a local tertiary care hospital were identified from the surgical database. A review of medical records was conducted to select two age-, gender- and procedure- matched control groups, one group with adolescent idiopathic scoliosis (AIS) and one group with cerebral palsy (CP). Control participants were selected based on having the closest age match (at time of surgery) to each participant with RTT. If more than one participant was an exact match, then participants were chosen in alphabetical order based on surname. Participants were included in the study if they had had spinal fusion surgery and received a morphine or morphine equivalent (e.g., hydromorphone) nurse or patient controlled analgesia (N/PCA) pump to manage postoperative pain.

A review of the medical records confirmed that all girls with RTT included in the study had significant motor impairments, were non-verbal, and had their pain assessed using an observational pain scale (rather than verbal self-report). Therefore, girls with CP were included in the study if the medical records also stated that they had severe motor impairments (defined as Gross Motor Function Classification System [GMFCS] levels III-V), and had their pain assessed using a non-verbal observational pain scale. Girls with AIS were included in the study if they did not have any comorbid conditions, motor or cognitive impairments, and were assessed for pain using a verbal self-report scale. Surgeries occurred from 1998 to 2012. Four girls with RTT initially identified received Fentanyl N/PCA pumps and were excluded from the study. Upon further review of their medical records, two girls with CP were determined to communicate verbally and were excluded and replaced with participants who met the inclusion criteria. This resulted in a final sample of 8 girls in each group.

Documentation of demographic data, surgical procedure, and extent of cognitive and motor impairment were recorded from physician notations. Postoperative medications (opioid N/PCA continuous infusion and bolus doses, adjuvant medications), delivery routes and pain assessment scores were obtained from the daily nursing logs. All participants received a continuous infusion of morphine (or equivalent) from their N/PCA which typically started out at a rate between 0.50 - 1.0mg/hour at a concentration of 2mg/ml. Bolus doses were available to all participants and typically started at a dose between 0.50 – 1.0 mg. The continuous infusion rate and bolus doses available were decreased over time until the N/PCAs were discontinued. The total opioid doses were calculated by adding the continuous infusion rate per hour plus total bolus doses per hour. Opioids were converted to morphine equivalents using standard equianalgesic conversions.¹⁶

To determine the extent to which daily/chronic medications might impact the post-operative pain management course, daily medication lists were collected for all participants. After extensive review, the only medication taken pre-operatively that would be expected to interact with the post-operative pain medications would be gabapentin. Gabapentin is long-acting and could enhance the effects of opioids¹⁷ and therefore may reduce the amount of opioids required in the post-operative period. Gabapentin was taken by one girl with RTT and one girl with AIS prior to spinal fusion surgery. To determine the impact of gabapentin

on the study findings, statistical analyses were conducted a second time with these two participants excluded.

Pain was assessed using either an observational numeric pain scale (RTT, CP groups) or a verbal self-report numeric pain scale (AIS group). The verbal report of pain was measured on a 6-point scale with 0 meaning “happy, no pain”, 1 meaning “hurts a little”, 2 meaning “hurts”, 3 meaning “hurts even more”, 4 meaning “hurts a whole lot”, and 5 meaning “hurts as much as you can imagine”. The observational pain scale measured pain on a 6-point scale with 0 meaning “no indicators of pain” were observed, 1 meaning “few indicators of pain” were observed, 2 meaning “mild indicators of pain” were observed, 3 meaning “moderate indicators of pain” were observed, 4 meaning “severe indicators of pain” were observed, and 5 meaning the “worst indicators of pain” were observed. Because nurses often recorded pain assessments as a range (e.g., 0-1, 2-3, etc.), pain assessment analyses were conducted using the daily maximum pain score recorded per participant. For example, if the most severe pain reported was written as “2-3” for a participant then the daily maximum pain assessment used for the study purposes would be “3”. Thus, mean pain assessment scores are the sum of the daily maximum pain score divided by the participant's length of stay (up to postop day 8).

The time frame for data extraction was purposefully large (1998-2012) in order to have a reasonable sample size of girls with RTT who had undergone spinal fusion surgery. The only hospital practice change noted during this time span was a reduction in the use of codeine over time. We assessed the impact of the large time frame as well as the use of codeine between groups. Data related to opioids and non-opioid adjuvant medications were analyzed two different ways. First, the dose data was calculated as mg/kg of drug administered in the postoperative period divided by the participant's length of stay up to postoperative day 8. Second, the data were calculated as mg/kg of drug given in the postoperative period divided by number of days on which the drug was administered. This second approach provided information related the average daily dose of the medications. Data on N/PCA morphine equivalent bolus doses were reported by total number of bolus doses administered overall as well as the number of N/PCA bolus doses given per day while the N/PCA was in place. All comparisons between groups were assessed using one-way analyses of variance (ANOVA). Due to the small sample size and the exploratory rather than confirmatory nature of this study, post hoc analyses were conducted using Fisher's least significant difference (LSD). Descriptive data are presented as mean, standard deviation, range (95% confidence interval), and n (%) as appropriate. Significance was set at $p < .05$.

Results

Demographic data and the nature of surgical procedures for the three groups are presented in Table 1. Post-operative complications are noted by group in Table 2. There were no statistically significant differences between groups in terms of age ($p = .98$), type of surgery (posterior vs. posterior/anterior fusion; $p = .35$), length of hospital stay (in days; $p = .12$) or days with N/PCA ($p = .49$). Patients with AIS had significantly heavier weights compared to patients with RTT (95% CI 9.24 to 27.61; $p = .001$) and CP (95% CI 11.03 to 29.39; $p = .001$; see Table 1); however, weight was controlled for by converting medication doses to mg/kg/day. Because of the long sampling time frame, we conducted preliminary analyses to

determine the impact of the year of surgery and differences in codeine use (a known practice change over time). We found no difference between groups in the amount of codeine ordered ($F(2,21)=.83$, $p=.45$). The groups did not differ by year the surgery was performed ($F(2,21)=.52$, $p=.60$) and there was no significant correlation between year of surgery and total opioids delivered ($r=-.03$, $p=.90$). When grouping year of surgery into two 7-year epochs (1998-2004; 2005-2012) an independent samples t-test detected no significant difference in total opioids given ($t(22)=-.20$, $p=.67$) or on average pain scores in the first 5 post-operative days ($t(21)=-.35$, $p=.73$).

There was a significant main effect for number of spinal levels fused $F(2,21)= 34.93$, $p < .001$. Patients with AIS had significantly fewer spinal segments fused compared to girls with RTT (95% CI -7.40 to -4.10 ; $p < .001$) and girls with CP (95% CI -7.40 to -4.10 ; $p < .001$). Girls with RTT did not differ from girls with CP in the number of spinal segments fused (95% CI -1.65 to 1.65 ; $p = 1.0$; see table 1). One girl with RTT had an anterior/posterior fusion with a transthoracic approach and two girls with CP had anterior/posterior fusions – one with a transthoracic approach and one with a thoracic approach. Segments fused were not double counted for anterior/posterior fusions.

Data related to opioids and non-opioid adjuvant medications were analyzed in terms of mg/kg divided by length of stay (displayed in Table 3) as well as by mg/kg divided by number of days the drug was administered (average daily dose; displayed in Table 4). Because these two approaches yielded nearly identical results, findings are based on analysis for mg/kg by length of stay. There was a statistically significant main effect for morphine equivalent opioids by length of stay $F(2,21)= 6.13$, $p = .008$. Post hoc comparisons indicated that girls with RTT received, on average, significantly less opioids compared to girls with AIS (95% CI -0.34 to -0.08 ; $p = .001$) and girls with CP (95% CI -0.27 to -0.02 ; $p=.01$). There was no difference in total opioids delivered for girls with CP and girls with AIS (95% CI -0.04 to 0.19 ; $p=.22$; See Table 3 and Figure 1). Girls with RTT received significantly less total opioids compared to girls with AIS on postoperative day 1 (95% CI -0.44 to -0.02 ; $p=.03$), day 2 (95% CI -0.62 to -0.01 ; $p=.04$), day 3 (95% CI -0.56 to -0.04 ; $p=.03$), and day 4 (95% CI -0.46 to -0.05 ; $p=.02$). Opioids by day did not differ significantly in any other group comparisons, with one exception on postoperative day 7 when girls with AIS received less opioids compared to girls with CP (95% CI -0.26 to -0.03 ; $p=.02$).

There was a statistically significant main effect for total number of N/PCA bolus doses of morphine equivalent opioids given in the postoperative period $F(2,24)= 4.208$, $p=.03$. Post hoc comparisons (LSD) indicated that girls with RTT, on average, received fewer bolus doses of opioids compared to girls with AIS (95% CI -96.42 to -14.83 ; $p=.01$). There was statistical evidence for a marginal effect indicating that girls with RTT also received fewer bolus doses compared to girls with CP (95% CI -79.05 to 2.55 ; $p=.06$). There was no mean difference in number of bolus doses between girls with CP and girls with AIS (95% CI -23.42 to 58.17 ; $p=.39$; See Table 3). Additionally, there was evidence for a marginal main effect for N/PCA bolus doses per day of morphine equivalent opioids $F(2,21)= 3.20$, $p=.06$. Post hoc comparisons again indicated that girls with RTT, on average, received significantly fewer bolus doses of opioids per day compared to girls with AIS (95% CI -28.79 to -2.79 ;

$p = .02$). There were no statistically significant differences between the other group comparisons.

Groups did not differ statistically on mean acetaminophen, diazepam, propofol, or midazolam delivered during inpatient postoperative recovery (Table 3). However, there was a significant main effect for the delivery of PRN hydroxyzine $F(2,21) = 5.34$, $p = .01$ (see Table 3). Post hoc comparisons (LSD) indicated that, on average, girls with RTT received significantly less hydroxyzine compared to girls with AIS (95% CI -1.24 to -0.24 ; $p = .006$). Girls with CP also received significantly less hydroxyzine compared to girls with AIS (95% CI 0.10 to 1.10 ; $p = .02$). Girls with RTT did not differ significantly from girls with CP in the amount of hydroxyzine received (95% CI -0.64 to 0.36 ; $p = .57$). Although differences were not statistically significant, on average girls with RTT received less of all adjunct medications for pain relief (see Table 3).

There was an overall main effect for maximum daily pain recorded during the postoperative inpatient stay ($F(2,20) = 9.42$, $p = .001$). Girls with RTT exhibited significantly fewer observational indicators of pain compared to the self-report pain assessment scores of girls with AIS (95% CI -1.67 to -0.54 ; $p = .001$) but pain scores did not differ significantly compared to the observational pain assessment scores for girls with CP (95% CI -0.81 to 0.31 ; $p = .36$). Observational pain assessment scores for girls with CP were also significantly lower compared to the self-report pain assessment scores of girls with AIS (95% CI -1.40 to -0.31 ; $p = .004$). Descriptively, however, and of note, was that over time it appeared that the maximum pain ratings for the RTT sample increased relative to the other two groups. Mean pain assessment scores for each group are presented in Table 3 and pain scores by group by postoperative day are presented in Figure 2.

Analyses were repeated with two participants excluded to determine if their daily gabapentin medication impacted the study findings. The between group difference for total opioids administered held ($F(2,19) = 6.27$, $p = .008$). Post-hoc comparisons also remain unchanged. Girls with RTT received, on average, significantly less opioids compared to girls with AIS (95% CI -0.37 to -0.09 ; $p = .002$) and girls with CP (95% CI -0.27 to -0.007 ; $p = .04$). There was no difference in total opioids delivered for girls with CP and girls with AIS (95% CI -0.04 to 0.22 ; $p = .17$). The between group differences for total opioids administered by day trended in the same direction but was greater than the $p < .05$ set significance. This might be expected due to reduction in power with reduced sample size. The between group difference for total number of bolus doses held ($F(2,19) = 3.42$, $p = .05$). Post-hoc comparisons also remain unchanged. Girls with RTT received significantly fewer bolus doses compared to girls with AIS (95% CI -100.75 to -10.68 , $p = .018$). The between group difference for total hydroxyzine held ($F(2,19) = 4.73$, $p = .02$). Post-hoc comparisons remained unchanged. Girls with RTT received significantly less hydroxyzine compared to girls with AIS (95% CI -1.34 to $-.22$, $p = .009$).

The between group differences for average pain scores held despite exclusion of the two participants taking gabapentin ($F(2,19) = 12.02$, $p < .001$). Post-hoc comparisons remained unchanged. Girls with RTT exhibited significantly fewer observational indicators of pain compared to the self-report pain assessment scores of girls with AIS (95% CI -1.78 to

–0.67; $p < .001$) but pain scores did not differ significantly compared to the observational pain assessment scores for girls with CP (95% CI –0.79 to 0.28; $p = .34$). Observational pain assessment scores for girls with CP were also significantly lower compared to the self-report pain assessment scores of girls with AIS (95% CI –1.51 to –0.44; $p = .001$).

Discussion

In this study we found evidence for a RTT-specific difference in postoperative pain management following spinal fusion surgery. Girls with RTT received significantly fewer total doses of opioids compared to girls with CP who had comparable motor and cognitive impairments as well as compared to typically developing girls with AIS. As designed, the study does not shed any light on the possible reasons for the documented difference. As reviewed, there are several possibilities including a belief that girls with RTT are insensitive to pain (which would be an understandable perspective given the diagnostic criteria for the syndrome includes reduced pain sensitivity), and therefore experience less pain. The daily pain ratings, however, seem to contradict this as the RTT group's pain was rated in the same range as the two comparison groups. It could be considered that girls with RTT experience chronic pain preoperatively impacting their expression of acute pain post-operatively. Girls with CP; however, are at risk for all the same chronic pain conditions as girls with RTT (e.g., gastrointestinal pain, musculoskeletal pain)^{18,19} and all three groups (including girls with AIS) may experience chronic pain related to severe scoliosis.²⁰ Thus, chronic pain is unlikely to account for the differences between groups.

There is also the possibility that the observed differences in postoperative opioid analgesic management were based on the notion that there is a reduced analgesic need in RTT. This is the argument advanced, in part, in several of the prior case studies.¹¹⁻¹⁴ There is pre-clinical evidence that MeCP2 plays an important role in the development of nociceptive pathways, affecting mu opioid receptor (MOR) regulation²¹ which could theoretically impact the way girls with RTT respond to opioids. However, it remains unknown whether and how the pre-clinical models of RTT relate to the pain phenotype of patients with RTT.

In their postoperative study of RTT, Karmanioliou et al.² did not detect differences in postoperative pain management of girls with RTT undergoing scoliosis surgery when comparing the experiences of 24 girls to existing pediatric postoperative guidelines. While this is an encouraging finding, the current sample, although smaller, used matched control groups (developmentally typical and developmentally disabled) on age, gender and surgical procedure - perhaps increasing the ability to detect differences specific to the surgical procedure and its postoperative analgesic management.

A tangential outcome of this study is the clear discordance between pain assessment scores and severity of surgical procedure. The groups with RTT and CP had significantly more spinal segments fused compared to the group with AIS. Additionally, one girl with RTT and two girls with CP had anterior/posterior spinal fusions whereas all girls with AIS had posterior-only spinal fusions. Potentially, this means that girls with RTT and CP had more invasive procedures, on average, compared to girls with AIS; yet, the non-verbal pain assessment scores in CP and RTT, on average, were significantly lower compared to the

verbal pain assessment scores of the girls with AIS. This finding highlights the difficult nature of assessing pain in non-verbal patient populations.

The data presented here are preliminary and descriptive and are intended only as the first steps toward characterizing post-surgical pain management in RTT. The data were collected retrospectively from existing medical records which limited our ability to assess additional information. For example, we did not have access to nurses' perceptions of pain management practices and we could not choose the pain assessment scales. The pain assessment scales differed between the non-verbal (CP and RTT) and verbal groups (AIS). This, in part, was the reason for including a second control group (CP) to provide a comparison group that was also assessed using an observational pain scale. All participants across groups had posterior spinal fusions with the exception of three individuals who had anterior/posterior spinal fusions introducing some degree of variability in the surgical approach. Group sample sizes were small which undoubtedly reduced statistical power; however, matching participants on age, gender, and surgical procedure increased the precision needed to detect differences between groups.

Further research is needed to determine whether the MeCP2 mutation underlying the RTT diagnosis impacts the way opioids are metabolized. Given the nature of RTT syndrome and its underlying pathophysiology, it is reasonable to speculate whether the mechanisms supporting nociceptive signaling are intact. MeCP2 is a crucial protein for neuronal development; the loss of which leads to profound neuronal dysfunction and abnormal brain development. The available evidence from preclinical investigations suggests reflexive pain circuitry is intact but that higher-order discriminatory behavior may be impaired (although there may be motor confounds in the behavioral assays making the interpretation of withdrawal latencies and related metrics difficult to interpret).²² Of relevance to nociceptive signaling pathways, MeCP2 expression is localized in the dorsal horn of the spinal cord, specifically in neurons, oligodendrocytes, and astrocytes with evidence of opposite effects depending on inflammatory (upregulation) or neuropathic (down regulation) pain models. As mentioned above, there is also preliminary evidence that MeCP2 may be important for mu opioid receptor (MOR) regulation, with increased MeCP2 activity resulting in hypermethylation of the genomic MOR promoter region and consequent reduced MOR protein expression.²¹ Taken together, it is plausible that through DNA methylation, MeCP2 plays an important role in the development and function of highly relevant components of nociceptive circuitry. The relation between the pre-clinical models, however, and the clinical pain phenotype is not well established (it has not, to our knowledge, been explicitly investigated).

Clinicians are reminded that recent work has documented a wide repertoire of pain expression in girls with RTT.⁶ Careful examination of the facial, vocal and overall motor behavior of girls with RTT may be required to determine the presence and severity of pain. There are many pain assessment tools available such as the Non-Communicating Children's Pain Checklist – Revised (NCCPC-R).²³ which are recommended for use in clinical practice for any nonverbal patient group with severe disabilities; of particular note there is a postoperative version.²⁴ In addition, parents and caregivers should be included in clinical discussions surrounding the pain experience of their daughter. Parents provide valuable

information when asked specific questions pertaining to the frequency, duration and intensity of their daughter's pain. The Pediatric Pain Profile (PPP),²⁵ is a tool to facilitate collecting pre-operative pain-related information specific to an individual patient with significant disabilities.

Overall, in an era of increasingly personalized medicine and the continued efforts to optimize postoperative analgesia, non-verbal patients with significant disabilities present a clinical challenge. RTT appears to be a syndrome for which more work is needed; many individuals with RTT will develop scoliosis and are therefore future surgical candidates. Improving our ability to detect pain in this patient group and tailor postoperative analgesic management should be a priority among the specialized providers that see patients with RTT. Clinical and bench science could be aligned around this practice problem by working to further clarify whether the *MECP2* mutation's exon location determines any difference in MOR expression and whether this translates into meaningful differences in the effects of opioids in patients with RTT.

Acknowledgements

Ethical approval was obtained prior to conducting this research study. This research was supported, in part, by The MAYDAY Fund and NIH Grant No. 44763 & 47201. The authors have no conflicts of interest to declare. The authors would like to thank Lynn Choromanski and Jennifer Carpenter for their technical assistance.

References

1. Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol*. 2010; 68(6):944–50. [PubMed: 21154482]
2. Karmanioliou I, Krishnan R, Galtrey E, Cleland S, Vijayaraghavan R. Perioperative management and outcome of patients with Rett syndrome undergoing scoliosis surgery: a retrospective review. *J Anesth*. 2015; 29(4):492–8. [PubMed: 25617158]
3. Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev*. 2002; 8:61–5. [PubMed: 12112728]
4. Down J, Geranton SM, Bebbington A, Jacoby P, Bahi-Buisson N, Ravine D, et al. Linking MECP2 and pain sensitivity: the example of Rett syndrome. *Am J Med Genetics*. 2010; 152A:1197–205. [PubMed: 20425824]
5. Symons FJ, Byiers B, Tervo R, Beisang A. Parent-reported pain in Rett syndrome. *Clin J Pain*. 2013; 29(8):744–6. [PubMed: 23835769]
6. Barney CC, Feyma T, Beisang A, Symons FJ. Pain experience and expression in Rett syndrome: Subjective and objective measurement approaches. *J Dev Phys Disabil*. 2015; 27(4):417–29. [PubMed: 26425056]
7. Downs J, Torode I, Ellaway C, Jacoby P, Bunting C, Wong K, Christodoulou J, Leonard H. Family satisfaction following spinal fusion in Rett syndrome. *Dev Neurorehabil*. 2016; 19(1):31–37. [PubMed: 24724550]
8. Leonard H, Ravikumara M, Baikie G, Naseem N, Ellaway C, Percy A, et al. Assessment and management of nutritional growth in Rett Syndrome. *J Pediatr Gastroenterol Nutr*. 2013; 57(4):451–60. [PubMed: 24084372]
9. Manrique D, Sato J, Anastacio EM. Postoperative acute respiratory insufficiency following adenotonsillectomy in children with neuropathy. *Int J Pediatr Otorhinolaryngol*. 2008; 72(5):587–91. [PubMed: 18295353]
10. Malviya S, Voepel-Lewis T, Tait AR, Merkel S, Lauer A, Munro H, et al. Pain management in children with and without cognitive impairment following spine fusion surgery. *Paediatr Anaesth*. 2001; 11(4):453–8. [PubMed: 11442864]

11. Khalil SN, Hanna E, Farag A, Armendartz G. Rett syndrome: anaesthesia management. *Paediatr Anaesth*. 2002; 12(4):375. [PubMed: 11982851]
12. Konarzewski WH, Misso S. Rett syndrome and delayed recovery from anaesthesia. *Anaesthesia*. 1994; 49(4):357.
13. Konen AA, Joshi GP, Kelly CK. Epidural analgesia for pain relief after scoliosis surgery in a patient with Rett's syndrome. *Anesth Analg*. 1999; 89:451–2. [PubMed: 10439765]
14. Kumar A, Chaudhuri S, Budania LS, Joseph TT. Peculiar breathing in Rett syndrome: Anesthesiologist's nightmare. *J Anaesthesiol Clin Pharmacol*. 2015; 29(2):278–80.
15. Rumbak DM, Mowrey W, Schwatz S, Sarwahi V, Djukic A, Killinger JS. Spinal fusion for scoliosis in Rett syndrome with an emphasis on respiratory failure and opioid usage. *J Child Neurol*. 2016; 31(2):153–158. [PubMed: 25991642]
16. McCaffery, M., Pasero, C. *Pain: Clinical Manual Second Edition*. University of Michigan; Mosby: 1999.
17. Eckhardt K, Ammon S, Hofmann U, Riebe A, Gugeler N, Mikus G. Gabapentin enhances the analgesic effect of morphine in healthy volunteers. *Anesth Analg*. 2000; 91(1):185–191. [PubMed: 10866910]
18. Barney CC, Krach LE, Rivard PF, Belew JL, Symons FJ. Motor function predicts parent-reported musculoskeletal pain in children with cerebral palsy. *Pain Res Manag*. 2013; 18(6):323–327. [PubMed: 24308022]
19. Ramstad K, Jahnsen R, Skjeldal OH, Diseth TH. Characteristics of recurrent musculoskeletal pain in children with cerebral palsy aged 8 to 18 years. *Dev Med Child Neurol*. 2011; 53:1013–1018. [PubMed: 22014321]
20. Weinstein SL, Dolan LA, Spratt KF, Peterson KK, Spoonamore MJ, Ponseti IV. Health and function of patients with untreated idiopathic scoliosis. *JAMA*. 2003; 289(5):559–567. [PubMed: 12578488]
21. Hwang CK, Song KY, Kim CS, Choi HS, Guo XH, Law PY, et al. Epigenetic programming of μ -opioid receptor gene in mouse brain is regulated by MeCP2 and brg1 chromatin remodeling factor. *J Cell Mol Med*. 2009; 13(9B):3591–615. [PubMed: 19602036]
22. Samaco RC, Fryer JD, Ren J, Fyffe S, Chao HT, Sun Y, et al. A partial loss of function allele of methyl-CpG-binding protein 2 predicts a human neurodevelopmental syndrome. *Hum Mol Genet*. 2008; 17(12):1718–27. [PubMed: 18321864]
23. Breau LM, McGrath PJ, Camfield CS, Finley GA. Psychometric properties of the non-communicating children's pain checklist-revised. *Pain*. 2002; 99(1-2):349–57. [PubMed: 12237214]
24. Breau LM, Finley GA, McGrath PJ, Camfield CS. Validation of the non-communicating children's pain checklist-postoperative version. *Anesthesiology*. 2002; 96(3):528–35. [PubMed: 11873023]
25. Hunt A, Goldman A, Seers K, Crichton N, Mastroiannopoulou K, Moffat V, et al. Clinical validation of the paediatric pain profile. *Dev Med Child Neurol*. 2004; 46(1):9–18. [PubMed: 14974642]

What is already known

The literature related to pain and postoperative management in Rett syndrome is equivocal; case study evidence indicates possible reduced pain sensitivity and reduced need for analgesia whereas direct behavioral pain assessment findings indicate evidence for preserved pain expression which would suggest conventional analgesic management is warranted.

What this article adds

The case-controlled study documents discrepancies in postoperative pain management specific to patients with Rett syndrome following spinal fusion surgery compared to age- and procedure-matched patients with and without developmental disability but without Rett syndrome.

Figure 1.

Comparison of opioid use by postoperative day for girls with RTT, AIS, and CP. Day 0 has been adjusted to account for the number of hours each patient spent postoperatively rather than a full 24 hours. Error bars represent standard deviation. * $p < .05$ compared to RTT.

Figure 2.

Mean postoperative pain scores by day for girls with RTT, AIS, and CP. Scores reflect the highest recorded pain score for each day. Girls with RTT and CP were assessed observationally and girls with AIS were assessed via verbal self-report (both scored 0-5). Error bars represent standard deviation. Note: Pain assessment scores were not available for one patient with RTT.

Table 1

Participant demographics and surgery related information

	RTT (n=8)	AIS (n=8)	CP (n=8)
Age (years)	13.15 ± 1.89	13.12 ± 1.88	13.10 ± 1.97
Weight (kg)	34.03 ± 10.41	52.45 ± 10.32 *	32.24 ± 4.38
Type of Spinal Fusion:			
Posterior	7 (88)	8 (100)	6 (75)
Posterior/Anterior	1 (12)	0 (0)	2 (25)
Number of Spinal Levels Fused	15.25 ± 1.04	9.50 ± 2.45 *	15.25 ± 0.71
Length of Stay (days)	8.50 ± 3.96	5.63 ± 0.92	7.38 ± 2.13
Days with PCA	3.38 ± 1.06	3.75 ± 1.28	4.13 ± 1.36

RTT = Rett syndrome; AIS= adolescent idiopathic scoliosis; CP= cerebral palsy

*
p = 0.01 compared to girls with RTT and CP. Data are expressed as mean ± SD or n (%).

Table 2

Post-operative complications noted in discharge summary.

Participant	RTT	AIS	CP
1	Blood transfusion, ventilated until PO day 2, PICU until PO day 2, seizures	None	Blood transfusion, urinary tract infection
2	None	Mild fever, low hemoglobin	Intubated until PO day 2, blood transfusion, pain poorly controlled, respiratory issues, decreased level of consciousness
3	Intubated until PO day 4, pneumonia developed on PO day 4	None	Intubated until PO day 1, significant respiratory difficulties – on CPAP, respiratory tract infection may have been present pre-operatively
4	None	None	Intubated until PO day 2, in PICU until PO day 2 due to somnolence
5	Constipation, mild generalized seizure, mild fever	None	None
6	None	None	None
7	None	None	Seizure activity, low fever
8	None	None	None

RTT = Rett syndrome; AIS= adolescent idiopathic scoliosis; CP= cerebral palsy; PO= post-operative; CPAP= continuous positive airway pressure.

Group comparison of total and daily P/NCA bolus doses, total medications given (mg/kg) by length of inpatient stay (up to postoperative day 8), and pain intensity scores recorded on the day of surgery and the 8 postoperative days following surgery.

Table 3

Drug	RTT (n=8) M(SD) range [95% CI]	AIS (n=8) M(SD) range [95% CI]	CP (n=8) M(SD) range [95% CI]	p=
TOTAL PCA bolus doses (#)	42.63 (17.84) 17-68 [27.71, 57.54]	98.25 (52.77) 40-210 [54.13, 142.37]	80.88 (38.93) 24-123 [48.32, 113.42]	.03
PCA bolus doses per day with PCA	13.16 (5.02) 5.67-20.00 [8.97, 17.36]	28.95 (19.69) 13.33-70.00 [12.50, 45.41]	20.31 (7.50) 6.00-30.00 [14.04, 26.59]	.06
Opioids (Morphine equivalent)	0.26 (0.10) 0.11-.42 [0.17, 0.34]	0.47 (0.13) 0.30-0.69 [0.36, 0.57]	0.40 (0.14) 0.25-0.66 [0.28, 0.52]	.008
Acetaminophen	30.51 (11.20) 8.80-41.16 [21.15, 39.87]	41.86 (10.02) 25.28-53.09 [33.49, 50.24]	39.11 (9.91) 24.32-53.03 [30.82, 47.40]	.10
Diazepam (Valium)	0.08 (0.07) 0.01-0.24 [0.02, 0.14]	0.13 (0.09) 0.01-0.26 [0.05, 0.21]	0.13 (0.13) 0.00-0.41 [0.02, 0.24]	.55
Hydroxyzine	0.07 (0.13) 0.00-0.34 [-0.03, 0.18]	0.81 (0.73) 0.00-1.75 [0.20, 1.42]	0.21 (0.38) 0.00-0.95 [-0.11, 0.53]	.01
Propofol	0.25 (0.42) 0.00-0.96 [-0.11, 0.60]	0.00 (0.00)	0.25 (0.46) 0.00-1.33 [-0.14, 0.64]	.31
Midazolam (Versed)	0.01 (0.04) 0.00-0.10 [-0.02, 0.04]	0.00 (0.00)	0.004 (0.01) 0.00-0.03 [-0.004, 0.01]	.50
Mean maximum daily pain (scored 0-5)	1.57 (0.36) 1.13-2.11 [1.23, 1.90]	2.67 (0.74) 1.83-4.00 [2.05, 3.29]	1.82 (0.35) 1.25-2.38 [1.53, 2.11]	.001

RTT = Rett syndrome; AIS= adolescent idiopathic scoliosis; CP= cerebral palsy; CI= 95% confidence interval

Table 4

Group comparison of total medications given (mg/kg) by number of days on which the medication was administered (average daily doses).

Drug	RTT (n=8) M(SD) range [95% CI]	AIS (n=8) M(SD) range [95% CI]	CP (n=8) M(SD) range [95% CI]	p=
Opioids (Morphine equivalent)	0.27(0.10) 0.11-.42 [0.18,0.35]	0.49(0.12) 0.36-0.69 [0.40,0.59]	0.42(0.12) 0.26-0.66 [0.33,0.52]	.002
Acetaminophen	37.62(8.20) 23.47-46.31 [30.76, 44.47]	44.46(9.32) 31.60-54.27 [36.67, 52.25]	41.63(9.99) 27.80-58.33 [33.28, 49.98]	.35
Diazepam (Valium)	0.14(0.07) 0.05-0.27 [0.09, 0.20]	0.18(0.09) 0.06-0.29 [0.11, 0.25]	0.18(0.12) 0.00-0.41 [0.08, 0.29]	.65
Hydroxyzine	0.24(0.35) 0.00-0.90 [-0.06, 0.53]	1.10(0.99) 0.00-2.45 [0.27, 1.93]	0.42(0.66) 0.00-1.52 [-0.13, 0.98]	.06
Propofol	1.16(1.89) 0.00-4.30 [-0.42, 2.74]	0.00(0.00)	0.68(1.28) 0.00-3.18 [-0.39, 1.75]	.23
Midazolam (Versed)	0.02(0.06) 0.00-0.16 [-0.03, 0.07]	0.00(0.00)	0.02(0.05) 0.00-0.13 [-0.02, 0.06]	.50

RTT = Rett syndrome; AIS= adolescent idiopathic scoliosis; CP= cerebral palsy; CI= confidence interval