

# Acute Pain Relief After Mantram Meditation in Children With Neuroblastoma Undergoing Anti-GD2 Monoclonal Antibody Therapy

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**Summary:** Nonpharmacologic, mind-body interventions are used to reduce anxiety in pediatric patients. Anti-ganglioside GD2 monoclonal antibody (anti-GD2 MoAb 3F8) therapy is the standard of care for high-risk neuroblastoma and pain is its major side effect. We performed a retrospective analysis of children undergoing anti-GD2 MoAb 3F8 treatment who received guided meditation. Meditation involved concentrating on the repetition of rhythmic, melodic sounds purported to slow breathing and induce a relaxation response. A total of 71% patients completed a session at first (n = 19) or second attempt (n = 5). Patients received fewer analgesic doses to manage anti-GD2 MoAb 3F8-induced pain when participating in meditation (n = 17, mean = -0.4 dose,  $P < 0.01$ ). Mantram meditation is a feasible outpatient intervention associated with reduced analgesic requirements.

**Key Words:** pain, neuroblastoma, meditation, children, mantram

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Meditation is an ancient self-administered technique that has recently been shown to be an effective modulator of pain in adults.<sup>1–4</sup> It has also been associated with positive thinking, reduced anxiety, and improved mood among adults,<sup>5–8</sup> although its role for pain relief in young children is unknown. Mantram is a type of meditation that places attention on the rhythmic, melodic repetition of key sounds that slow down or prolong the breath, giving the practitioner better control over autonomic breathing. Despite its antiquity and prevalence in eastern cultures, it is a lesser known form of meditation in the West, recently earning popularity and arousing scientific interest in its therapeutic value. Mantram is hypothesized to induce a relaxation response, thereby enhancing self-control over sensations, such as pain. Mantram meditation is highly structured and because it is vocal in nature it may be more easily learned, sustained, monitored, and evaluated than other forms of meditation. Because of its simplicity, this form of meditation has the potential to be intuitively and easily memorized by young children, without the need to stay still or silent for long periods of time.

Anti-ganglioside GD2 monoclonal antibody (anti-GD2 MoAb 3F8) has become the standard of care of high-risk metastatic stage 4 neuroblastoma.<sup>9,10</sup> GD2 is an

adhesion molecule abundant not only on neuroblastoma but also on neurons, skin cells, and myelin sheaths of peripheral pain fibers. Through antibody-dependent cell cytotoxicity and complement-mediated cytotoxicity, anti-GD2 antibodies achieve potent antitumor effects. However, because of the presence of GD2 on pain fibers, acute pain is the most common and severe morbidity, with grade 2-3 being reported for all anti-GD2 antibodies.<sup>9,11</sup> Pharmacologic interventions other than general anesthesia have managed only to sedate patients, but are unable to relieve these intense pain side effects. The opioid analgesics routinely used in an attempt to relieve pain are associated with frequent and significant adverse effects including respiratory depression, dysphoria, constipation, urinary retention, pruritus, and withdrawal. Nonpharmacologic interventions may complement or reduce opioid use. At Memorial Sloan-Kettering Cancer Center (MSKCC), several behavioral programs including dance therapy, play therapy, music therapy, and hypnotherapy have been implemented to reduce anxiety related to disease or to treatment among children and adolescents with cancer, including those receiving the anti-GD2 MoAb 3F8. Here we report the results of a retrospective analysis of the feasibility and efficacy of Mantram meditation in patients undergoing anti-GD2 MoAb 3F8 immunotherapy at MSKCC.

## MATERIALS AND METHODS

### Overview

The records from patients with high-risk neuroblastoma undergoing anti-GD2 MoAb 3F8 therapy at MSKCC during a 10-month period from 2010 to 2011 were reviewed with approval by the Institutional Review Board. These patients were treated on 1 of the 3 MSKCC IRB protocols: 03-077 (ClinicalTrials.gov NCT00072358), 09-011 (ClinicalTrials.gov NCT00877110), and 09-161 (ClinicalTrials.gov NCT01183897). All patients received subcutaneous injections of granulocyte-macrophage colony-stimulating factor (250 to 500 mg/m<sup>2</sup>/d × 10 d) plus intravenous infusion of anti-GD2 MoAb 3F8 (20 to 80 mg/m<sup>2</sup>/d × 5 d). Antihistamines and opioids were usually given before anti-GD2 MoAb 3F8 as previously described.<sup>12</sup> anti-GD2 MoAb 3F8 was administered intravenously over 30 minutes in the outpatient clinic. Pain started predictably in all patients 15 to 20 minutes into the infusion. The pain was usually visceral, starting in the abdomen, and spreading to the spine, extremities, and skull. In general, at the onset of pain, patients developed tachycardia, and received additional intravenous opioids (hydromorphone), which were administered by nurses experienced in 3F8 administration, but who were uninvolved in the application of the Mantram therapy. The nonpharmacologic methods offered

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to parents and children included music therapy, play therapy, dance therapy, and Mantram meditation. These interventions were generally applied before anti-GD2 MoAb 3F8 infusion. The exact timing of the Mantram sessions relative to anti-GD2 MoAb 3F8 infusion and the number of sessions offered to each child varied, as participation was voluntary on a day-to-day and cycle-to-cycle basis. In our analysis, we considered only children who participated in the Mantram meditation and no other nonpharmacologic interventions before treatment.

### Mantram Meditation Procedures

Mantram meditation was offered to families several days a week by experienced instructors. In many instances, parents, translators, and family members also participated. A single specific Mantram (“RaMaDaSa, Guru Ram Das and I Am”) soundtracks provided by Dr Joseph Michael Levy) was played on an MP3 player in the background while an experienced meditation teacher taught and led the Mantram. These Mantram are used traditionally to build self-esteem, peace, and resilience. Mudras (hand gestures) and gentle breathing patterns (left nostril breathing, long exhalation, alternate nostril breathing) were interspersed with Mantram to help relieve tension and enhance relaxation and focus. On an average, the meditation instructor stayed with the patient for approximately 30 minutes.

### Measures of Feasibility and Efficacy

Traditionally, 11 minutes of Mantram is recommended to achieve a relaxation response and because this was considered reasonable for young children, we defined a complete Mantram session as 11 minutes of vocalized sound accomplished by the patient. We assessed feasibility of Mantram meditation by analyzing the number of patients that were able to complete a session at first or second attempt, and the total number of completed sessions relative to the total number of sessions attempted. In the anti-GD2 MoAb 3F8 trials at MSKCC, pain is assessed by experienced nurses, and quantitated by the number of analgesic rescues given.<sup>12</sup> Questionnaires and self-administration of medication are not used. Therefore, to evaluate efficacy (the effect of Mantram meditation on pain), we analyzed peak heart rates and the number of analgesic rescues during anti-GD2 MoAb 3F8 treatment. A dose of analgesic was defined as 0.015 mg/kg hydromorphone. We compared outcomes from Mantram to preceding non-Mantram treatment cycles of the same patient. The data of any given session were matched to the same day of the week in the cycles before exposure to Mantram meditation. This was done because of the observed variation in heart rates and analgesic requirements during the course of 1 anti-GD2 MoAb 3F8 treatment cycle. Statistical analysis was performed using 2-tailed paired *t* tests for significance.

Although for feasibility we included children treated on 3 different anti-GD2 MoAb 3F8 protocols, for efficacy we restricted our evaluation to include only children treated on protocol 03-077 (ClinicalTrials.gov NCT00072358), all of whom received anti-GD2 MoAb 3F8 dose at 20 mg/m<sup>2</sup>/d, as this was the only group for which comparisons could be made. One cycle of treatment under this protocol consists of 5 consecutive days of antibody infusion per cycle, each cycle administered every 4 to 8 weeks.

## RESULTS

### Demographics

A total of 34 children with high-risk neuroblastoma undergoing anti-GD2 MoAb 3F8 treatment used Mantram meditation (Table 1). A total of 112 sessions were given over a 10-month period to children 3 to 14 years of age and of both sexes (26 male and 8 female). Most participants were English speaking; however, non-English speaking children also used Mantram.

### Feasibility

Most of the 34 children participating were able to do Mantram without difficulty. Of the 34 children (71%), 24 were able to complete 11 minutes of meditation at first (19/24) or second attempt (5/24). Ten patients were not able to complete 11 minutes with their first and only attempt. There was no difference in age between those who were able to complete an 11-minute meditation session at first attempt (mean age, 7.1 ± 2.2y), and those who did not (mean age, 7.9 ± 2.8y), *P* = 0.44. Overall, 75% (84/112) of the sessions offered were completed successfully. Participation in Mantram meditation continued for those children that regularly returned to the clinic for treatment, even though occasionally (11% of total) sessions fell short because of sedation from premedications. These results suggested that the learning curve for meditation among children undergoing anti-GD2 MoAb 3F8 treatment was sharp irrespective of age, and a single class might be adequate.

### Mantram and Pain Indicators

Routine pain scales are not used to measure pain in patients undergoing anti-GD2 MoAb 3F8 therapy because of difficulty of compliance and lack of validation for these scores in young patients experiencing severe acute pain. Instead, pain is quantitated through heart rate and the number of opioid rescues. Accordingly, the effect of Mantram on pain was also on the basis of these measures. Seventeen of the 34 children who used Mantram had prior anti-GD2 MoAb 3F8 treatment cycles on the same protocol (03-077) without Mantram administration, and hence were available for within-patient comparison. Table 2 summarizes the differences in peak heart rate and the number of analgesic rescues during anti-GD2 MoAb 3F8 infusion, with and without Mantram meditation. There were no statistically significant changes in peak heart rate in

TABLE 1. Demographics of Patients

|                  | Patients (N = 34) |
|------------------|-------------------|
| Female           | 8                 |
| Male             | 26                |
| Age (y)          |                   |
| Mean             | 7.6               |
| Range            | 3-14              |
| Primary language |                   |
| English          | 30                |
| Spanish          | 2                 |
| Italian          | 1                 |
| Greek            | 1                 |
| Mantram sessions |                   |
| Attempted        | 112               |
| Completed        | 84                |

**TABLE 2.** Summary of the Effect of Mantram Meditation on Peak Heart Rate and Number of Analgesic Rescues Administered to 17 Patients Undergoing 1 Cycle of anti-GD2 MoAb 3F8 Therapy on Protocol 03-077

| No. Patients                     | A          | B          | C          |
|----------------------------------|------------|------------|------------|
|                                  | N = 17     | N = 17     | N = 8      |
| No. Mantram sessions completed   | 1 ± 0      | 2 ± 1      | 3 ± 1      |
| Age (y)                          | 7.8 ± 2.6  | 7.8 ± 2.6  | 8.2 ± 2.3  |
| Peak HR                          |            |            |            |
| Pre-Mantram                      | 160 ± 17   | 156 ± 18   | 156 ± 20   |
| With Mantram                     | 157 ± 20   | 154 ± 21   | 152 ± 22   |
| Mean change                      | -3 ± 13    | -3 ± 11    | -5 ± 10    |
| P                                | 0.28       | 0.19       | 0.04       |
| No. analgesic doses administered |            |            |            |
| Pre-Mantram                      | 2.8 ± 1.1  | 2.9 ± 1.1  | 3.0 ± 1.1  |
| With Mantram                     | 2.4 ± 0.9  | 2.5 ± 1.0  | 2.6 ± 1.0  |
| Mean change                      | -0.4 ± 0.6 | -0.4 ± 0.7 | -0.3 ± 0.7 |
| P                                | 0.01       | < 0.01     | 0.02       |

Data are shown as mean values ± SD.

A: Effects of first Mantram meditation session on peak heart rate and analgesics administered.

B: Effects of all mantram meditation sessions on peak heart rate and analgesics administered.

C: Effects of Mantram meditation on subset of 8 patients that received 2 to 5 mantram meditation sessions during 1 cycle of anti-GD2 MoAb 3F8 treatment.

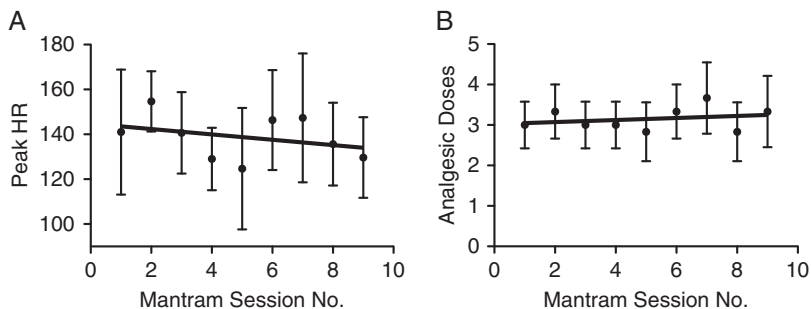
the first session in patients receiving a single session of Mantram; however, after an average of 3 sessions, a small but significant decrease in these heart rates was observed (mean decrease of 5 beats per minute  $P < 0.05$ ). When looking more closely at patients receiving  $\geq 5$  sessions ( $N = 3$ ), peak heart rate decreased inversely with the number of Mantram sessions (Fig. 1), although the trend was not statistically significant.

In contrast, a significant reduction in analgesic doses administered for anti-GD2 MoAb 3F8-associated pain was observed after the first Mantram session (decrease of 0.4 dose,  $P = 0.01$ ; Table 2). This represented a 14% decrease in the amount of hydromorphone administered to manage pain per day of treatment. Patients receiving 2 to 3 Mantram sessions per anti-GD2 MoAb 3F8 treatment cycle or multiple sessions over time consistently received fewer analgesic rescues (mean reduction of 0.3 to 0.4 dose,  $P < 0.01$  to 0.02), although no further reduction in analgesics was noted (Table 2, columns B and C).

**DISCUSSION**

Patients undergoing anti-GD2 therapy for neuroblastoma experience severe generalized pain that is poorly controlled with conventional analgesics, including opioids. Nonpharmacologic interventions have the potential to reduce pain, anxiety, and analgesic requirements associated with this treatment that is now considered standard of care for high-risk neuroblastoma. Mantram meditation therapy administered on an outpatient basis to children receiving anti-GD2 MoAb 3F8 immunotherapy was feasible and well tolerated by children of both sexes, aged 3 to 14 years with diverse language and ethnic backgrounds. Children could participate in Mantram while continuing to receive standard pharmacologic interventions to reduce pain as evaluated by their nurses. A total of 71% of children completed at least 11 minutes of Mantram. We found that Mantram meditation can be administered successfully to very young patients. Parents generally participated in the sessions and most reported an overall subjective improvement in their own well-being. After controlling for cycle-to-cycle variability, we observed that a single session of Mantram was associated with a small but significant decrease in the number of analgesic rescues given to reduce treatment-related pain. In a small cohort of patients, multiple Mantram sessions did not seem to show an incremental reduction in analgesics, although the effect was sustained, resulting in a decrease in the total overall narcotic usage. This is significant given that 1 cycle of anti-GD2 MoAb 3F8 treatment consists of 5 consecutive days of antibody infusion, and children are given 1 cycle of treatment every 4 weeks. A short, daily practice of Mantram could therefore signify a reduction by 2 doses a week or 0.6mg in an average 20 kg child. Although this may be a relatively small reduction in analgesics, it should be kept in mind that patients receiving anti-GD2 immunotherapy experience severe, generalized pain that is poorly controlled even with multiple doses of analgesics. We observed that pain in general was highest on the first day of therapy. This could represent anticipatory pain confounded by fear and anxiety and habituation throughout the week. It is noteworthy that in studies comparing nonmeditators and practicing meditators, meditation has been correlated with reduced anticipation and negative appraisal of pain measured by both reported pain and a decrease in activity in the cingulate cortex and prefrontal cortex.<sup>2,4,13</sup>

To the best of our knowledge, this is the first report on the effects of meditation in a clinical scenario that is consistently associated with severe pain in children. Despite the



**FIGURE 1.** Analysis of multiple Mantram meditation sessions on patient’s peak heart rate (HR) and analgesics ( $N = 3$ ). A, Peak HR as a function of meditation sessions, slope =  $-1.2 \pm 1.5$  bpm/session,  $P = 0.44$ . B, Analgesic doses as a function of meditation sessions, slope =  $0.0 \pm 0.1$  doses/session,  $P = 0.76$ .

small sample size, the results are encouraging and provide the basis for a rigorous, prospective study. It appears that the effects of Mantram meditation are immediate; however, a brief training followed by regular practice, ideally at home, may be the more beneficial scenario, partially by reducing anticipatory anxiety and fear. Furthermore, integration of other physiological measures of pain and inflammation will also provide insight into the mechanism of action of Mantram.

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