Appendix 3: Published papers

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Original Articles

A Systematic Review of the Therapeutic Effects of Reiki

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Abstract

Introduction: Reiki is an ancient form of Japanese healing. While this healing method is widely used for a variety of psychologic and physical symptoms, evidence of its effectiveness is scarce and conflicting. The purpose of this systematic review was to try to evaluate whether Reiki produces a significant treatment effect.
Methods: Studies were identified using an electronic search of Medline, EMBASE, Cochrane Library, and Google Scholar. Quality of reporting was evaluated using a modified CONSORT Criteria for Herbal Interventions, while methodological quality was assessed using the Jadad Quality score.
Data extraction: Two (2) researchers selected articles based on the following features: placebo or other adequate control, clinical investigation on humans, intervention using a Reiki practitioner, and published in English. They independently extracted data on study design, inclusion criteria, type of control, sample size, result, and nature of outcome measures.
Results: The modified CONSORT Criteria indicated that all 12 trials meeting the inclusion criteria were lacking in at least one of the three key areas of randomization, blinding, and accountability of all patients, indicating a low quality of reporting. Nine (9) of the 12 trials detected a significant therapeutic effect of the Reiki intervention; however, using the Jadad Quality score, 11 of the 12 studies ranked "poor."
Conclusions: The serious methodological and reporting limitations of limited existing Reiki studies preclude a definitive conclusion on its effectiveness. High-quality randomized controlled trials are needed to address the effectiveness of Reiki over placebo.

Introduction

There is growing interest in complementary and alternative medicine (CAM). The National Center for Complementary and Alternative Medicine (NCCAM) describes CAM as "a group of diverse medical and health care systems, practices, and products that are currently not part of conventional medicine."[1,2] Canadians spent an estimated $5.6 billion dollars out of pocket for CAM expenditures in the 12 months ending June 2006 compared to almost $2.8 billion in 1997.[3] Both Gordon[4] and Schiller[5] suggest that the awareness, use, and integration of CAM are beginning to shift from the marginal fringes to the mainstream of care.[6]

In a 2007 NCCAM survey, 0.5% of the United States general adult population reported having used Reiki therapy.[1,7]

Reiki is a therapy that claims to provide healing energy to recharge and rebalance the human energy fields, creating optimal conditions needed by the body's natural healing system.[6] Reiki, which is the Japanese term for "universal life energy," is believed to have originated thousands of years ago in Tibet and was re-established in the 1800s after having been forgotten, by Dr. Mikao Usui, a Japanese monk.

Energy-based healing interventions have been found throughout history:

- Hippocrates referenced the "biofield" of energy flow from people's hands,
- The Indian Chakra system is based on energy centers in the body, and
- Eastern energy practices such as *qigong* rely on the breath to balance the body's energy field

Studies have suggested that Reiki, classified by the NCCAM as a biofield energy therapy, reduces anxiety and depression and increases relaxation and comfort.[6,8] Also, Reiki is now widely used, mostly outside of mainstream medicine, to relieve pain, especially postoperative pain, and

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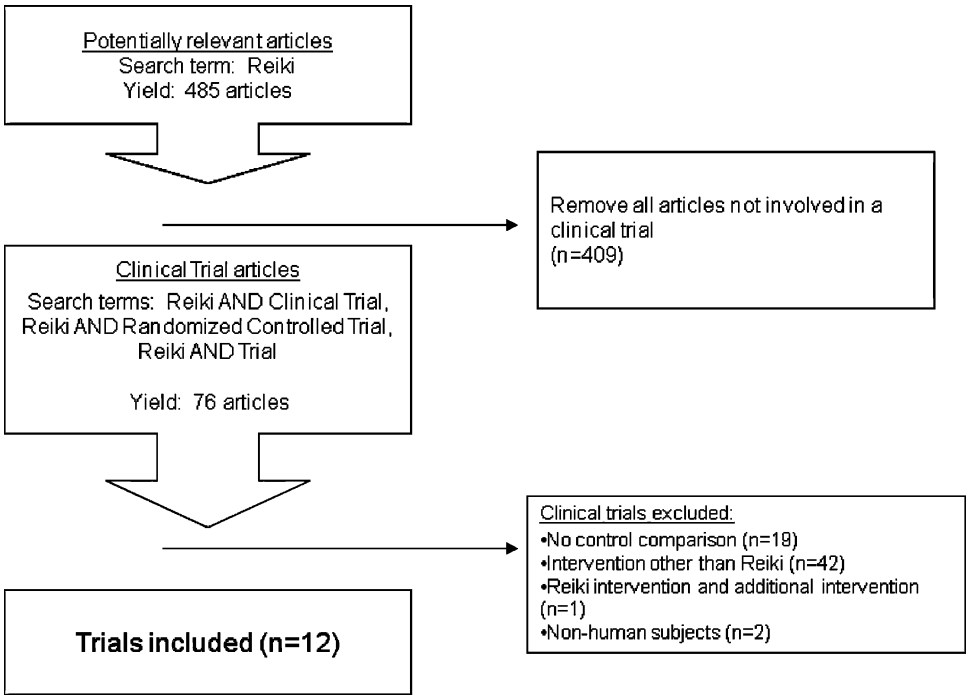

FIG. 1. Flow diagram of selection process.

to facilitate patient recovery. Reiki practice is administered through a gentle laying on of hands, or in absentia (i.e., remote Reiki where the Reiki practitioner is not present). Both types of practice are based on the assumption that the Reiki practitioner maintains a meditative presence and allows the Reiki energy to flow to where the patient needs it, in a nondirected and nondiagnostic manner.[6]

Reiki is typically taught in three levels (sometimes four, as the third level can be broken into part I and part II).[9] The focus of Reiki Level I is on recovering the natural healing abilities of the body. Reiki Level II teaches a deeper understanding of the energetic flow and introduces symbols to aid in treatment efficacy. The third level, Reiki Master, is almost completely focused on the inner spiritual development of the Reiki practitioner and most of the practices at this level concern themselves with the development of spiritual consciousness. Reiki Master training also focuses on the development of the skills needed to teach this work to other Reiki students. A necessary step in all levels is an "attunement" by a Reiki Master. The attunement (or initiation) process allows the Reiki energy to flow from the Reiki practitioner's hands to the patient. Without an attunement from a Reiki Master, a person cannot be said to be practicing Reiki, even if they learn the technical aspects of where to put their hands.

Energy-based healing encompasses a belief in a greater healing force and is inherent in many cultures. For example, healing approaches of the indigenous people of China, Tibet, Africa, Native America, and India are thought to work because of the members' belief in the expectation of healing.[10] However, these cultures maintain that healing, like illness, is not limited to those who believe in it, and that an illness is the result of a blockage in one's energy field. By introducing an energy-based intervention, the energy blockage is believed to be removed and this is believed to serve to rebalance the body's energy field, which in turn rebalances the physical body.[10]

If there is more to healing than belief, these effects should be able to be measured. Current scientific thinking indicates that the best way to measure the true effect of a biomedical intervention requires proper randomization, control, blinding, and concealment. These processes decrease the likelihood of bias and ensure internal study validity to help determine whether healing claims are more than belief.[10] While Reiki itself is not a biomedical intervention, it is used in the treatment of a variety of psychologic and physical symptoms, which might otherwise be treated with biomedical interventions (e.g., pharmaceutical substances). In this regard, its efficacy needs to be proven.

Reiki proposes to heal the whole patient, and is not directed solely to cure/relieve a single ailment. This whole system healing may require advanced techniques, such as nested qualitative research within a randomized controlled trial (RCT) to measure its effectiveness.[11] Given the complexity of measuring such effects, well-designed, well-executed clinical trials are a prerequisite, and any intentional deviations from the accepted "gold standard" RCT should be documented and explained.

Presently, despite increased interest and awareness, the results of specific studies on Reiki are inconclusive. The objectives of this systematic review were to (1) evaluate the quality of reporting of clinical trials using Reiki as the treatment modality and (2) evaluate the quality of existing evidence on the efficacy of Reiki in humans.

Methods

Literature review

Studies were identified by an electronic search of the Medline, EMBASE, and the Cochrane Library databases from their inception to the end of December 2008. The following search terms (Fig. 1) were employed in MEDLINE®:

Reiki, Reiki AND randomized controlled trial, Reiki AND clinical trial, Reiki AND clinical, Reiki AND trial. In EMBASE the following terms were used: Reiki.mp, Reiki AND randomized controlled trial, Reiki AND clinical trial. We employed the additional search terms to eliminate all the studies that were not clinical trials. We also used Google and Google Scholar to identify any articles or other publications that may have been missed. The reference lists of the selected articles were checked for additional studies that were not originally found in the search. In addition, given Reiki's Japanese origins, Medline and EMBASE were searched for Reiki studies published in Japanese; however, none were found.

Study selection and data extraction

Two researchers (S.V., V.G.) independently reviewed the list of unique articles for studies that fit the inclusion criteria (see below). The researchers were not blinded to the report name or author. Studies were selected based on the following inclusion criteria:

1. Presence of test group and control group (using either placebo, crossover, sham, or normal care)
2. Human subjects
3. A Reiki healer being responsible for the intervention
4. English language
5. Studies published up to December 2008.

Uncertainties over study inclusion were discussed between the researchers and resolved through consensus.

Quality assessment

Each study was assessed on whether or not it reported a statistically significant outcome measure for the Reiki intervention group. Each study was evaluated and counted only once regardless of how many statistically significant outcome measures it reported. The raw count was used to determine the percentage of studies yielding a statistically significant outcome.

We evaluated the accepted studies using a modified *CONSORT (Consolidated Standards of Reporting Trials) Criteria for Herbal Interventions.*[12] The original CONSORT was developed by a group of scientists and editors to improve the quality of reporting of RCTs.[13] The CONSORT for Herbal Interventions was developed to aid editors and reviewers in assessing the internal/external validity and reproducibility of herbal medicine trials, allowing an accurate assessment of safety and efficacy.[12] The authors chose the CONSORT for Herbal Interventions (HI) because it specifically breaks out important details about the Intervention, which adds important information about the Reiki trials. For example, the CONSORT for HI specifically details (1) dosage and frequency: Interpreted as how long the Reiki session lasted, and how many Reiki sessions were given; (2) practitioner: What is the level of training of the Reiki practitioner as well as the number of years of experience; (3) placebo or control: Reiki is usually administered by having a person present in a room with a patient (except not in the case of distant Reiki). Reiki placebo is important in determining whether the patients and assessors were blinded.

One researcher (S.V.) modified the herbal dosage components of the CONSORT for HI, to reflect the Reiki practitioner as the intervention instead of the herb (see Table 1 Original CONSORT for HI and Table 2 for modified CONSORT for HI).

For each CONSORT criterion, the 2 researchers independently assessed whether the reporting was adequate or not and scored the criterion as: Y (yes), N (no), P (partial), or NA (not applicable). We identified items that were adequately or not adequately reported according to the CONSORT definition of what is required for each item.

We considered the percentage of affirmative answers as the raw score for the internal validity. A percentage calculation was used to determine the proportion of CONSORT criteria that are adequately addressed. Items that were rated as NA were excluded from the analysis.

To assess the methodological quality of existing Reiki studies, we used the Jadad score. The Jadad score is the method most authors use to assess methodological quality.[14] This validated score ranges between 0 and 5. Studies are scored according to the presence of the three key methodological features of randomization, blinding, and accountability of all patients, including withdrawals (essentially subsets of the greater CONSORT criteria). Criteria are given a "0" or "1" score based on the absence or presence of the criteria. Scores are interpreted as: 0–2: poor methodological quality; 3–4 good methodological quality; and 5 excellent methodological quality.[15]

Results

A total of 485 unique articles were identified using Reiki as the only search term. To limit the articles to clinical trials only, we employed additional search terms as described above. As a result, study count was reduced to 76 (Fig. 1). The majority of these studies were either (a) small studies with no control arm, (b) descriptive case studies where researchers described a single patient Reiki intervention and/or recounted its history, or (c) studies using Therapeutic Touch (a similar but distinct therapy) and thus were excluded. Thirteen (13) studies fulfilled the aforementioned inclusion criteria. One study[16] was removed from the analysis because the intervention included two different types of practitioners (Reiki and Le Shan) and thus the results of the Reiki practitioner could not be isolated. This left a total of 12 studies to analyze.

Since four of the studies did not indicate the level of experience and/or the number of years of experience of the Reiki practitioner, the researchers attempted to contact the primary authors to obtain this information. The researchers were successful in contacting two of the authors,[17,18] and unsuccessful with authors for two of the studies.[19,20]

All of the studies differed in their studied populations and outcome measures. Of the 12 studies, 3 studies administered Reiki for physiological symptoms such as stroke recovery, seizure rate and heart rate and 9 studies administered Reiki for psychological symptoms such as anxiety and depression. A total of 31 different outcome measures were evaluated in the trials, none of which were used in more than 3 studies (Table 3). Hence, the heterogeneity of the studies' outcomes precluded a formal meta-analysis.

CONSORT reporting quality: Findings

The evaluators disagreed in 33% of the evaluations, with the majority of the disagreements resulting from a difference

Table 1. Original CONSORT Criteria for Herbal Interventions

Consort no.	*CONSORT criteria*	*Definition*
Title and abstract		
1	Word "random" or "randomization" used	Word "random" or "randomized" mentioned
Introduction		
2	Background (nature, scope, severity of problem)	Nature, scope, and severity of problem
Methods		
3a	Participants (eligibility)	Eligibility criteria for participants (must include exclusion criteria)
3b	Participants (setting and locations)	Settings and locations of participant interventions
4a	Intervention–Herbal medicine product name	Latin binomial name
4b	Intervention–Characteristics of herbal product	Type of product, concentration, method of authenticating raw product
4c	Intervention–Dosage	Description of type and frequency of herbal intervention
4d	Intervention–Qualitative testing	Product's chemical fingerprint and who performed the analysis
4e	Intervention–Placebo/control	Rationale for type of control/placebo used
4e	Intervention–practitioner	Description of practitioner: Training and practice level and years of experience
5	Primary and secondary objectives defined	Specific objectives and hypothesis
6	Outcomes	Clearly defined primary and secondary outcome measures
6b	Quality enhancement (if applicable)	If applicable, methods used to enhance the quality of measurements (e.g., multiple observers, training of assessors)
7	Sample size determination	How sample size was determined
7b	Interim analysis and stopping rules (if applicable)	If applicable, explanation of interim results and stopping rules
8	Randomization sequence allocation	Method used to generate the random sequence
8b	Details of restriction (if applicable)	If applicable, details of restriction
9	Allocation concealment	Method used to implement the random allocation sequence (e.g., numbered containers, central telephone)
10	Who generated the allocation sequence?	Who generated the allocation concealment
10b	Who enrolled the patients?	Who enrolled patients
10c	Who assigned the patients to the groups?	Who assigned patients to groups
11	Blinding (were participants and therapists blinded?)	Whether or not participants and therapists were blinded
11b	Blinding (were the assessors blinded?)	Whether or not assessors were blinded
11c	How was success of blinding evaluated (if applicable)	If applicable, how successful was blinding
12	Statistical methods	Statistical methods used to compare groups for primary outcome(s)
Results		
13	Participant flow	Flow of participants through each stage (diagram recommended). For each group report number of participants randomly assigned, receiving intended treatment, completing study protocol, and analyzed for primary outcome.
13b	Report of study violations (if applicable)	Report study violations with reasons
14	Recruitment	Dates defining the periods of recruitment and follow-up
15	Baseline data	Baseline demographic and clinical characteristics of each group (including concomitant medication, CAM use, etc.)
16	Numbers analyzed	No. of participants in each group
16b	Was it intention-to-treat analysis?	State whether analysis was "intention-to-treat" state numbers in absolute (e.g., 10/20).
17	Outcomes and estimations	State summary of effect for each group and effect size
17b	Precision of the effect size	State precision of the effect (i.e., 95% CI)
18	If applicable, ancillary analysis stated in protocol?	Address multiplicity by stating any other analyses performed including subgroup analyses and adjusted analyses
19	Adverse events (if applicable)	State any adverse events or side-effects in each intervention group
Discussion		
20	Interpretation	Interpretation of results taking into account study hypothesis, source of potential bias, and dangers associated with multiplicity of analyses
21	Generalizability	External validity of trial results; explain how treatment offered is similar in self-care/practice
22	Overall evidence	General interpretation of results in the context of current evidence

CAM, complementary and alternative medicine; CI, confidence interval.

Table 2. Study Scores

Consort no.	CONSORT criteria	Item no.	Individual studies												Sum of studies			
			17	25	23	21	22	19	20	26	27	24	18	*	Yes	No	Partly	NA
Title and abstract																		
1	Word "random" or "randomization" used	1	y	n	y	n	na	na	y	y	n	y	n	y	6	4	0	2
Introduction																		
2	Background (nature, scope, severity of problem)	2	y	y	y	p	y	p	y	y	p	y	p	p	7	0	5	0
Methods																		
3a	Participants (eligibility)	3	y	y	y	y	y	y	y	y	y	y	p	y	11	0	1	0
3b	Participants (setting and locations)	4	p	y	n	p	p	y	p	p	y	p	n	p	3	2	7	0
4c	Intervention–Dosage regimen	5	y	y	y	y	y	p	y	y	y	y	p	y	10	0	2	0
4e	Intervention–Control group	6	y	y	y	y	y	y	y	y	p	y	y	y	11	0	1	0
4f	Intervention–Practitioner	7	n	y	y	p	y	n	p	y	y	y	n	y	7	3	2	0
5	Primary and secondary objectives defined	8	y	y	y	y	y	y	y	y	y	y	y	y	12	0	0	0
6	Outcomes	9	p	y	p	y	n	y	y	y	y	p	y	y	8	1	3	0
6b	Quality enhancement of the outcome measurement	10	y	y	y	y	y	y	y	y	y	y	y	y	12	0	0	0
7	Sample size determination	11	n	y	n	y	n	n	y	y	n	n	n	n	4	8	0	0
7b	Interim analysis and stopping rules (if applicable)	12	na	na	na	na	na	na	na	na	na	na	na	na	0	0	0	12
8	Randomization sequence allocation	13	n	n	n	y	y	n	y	n	n	n	n	y	4	8	0	0
8b	Details of restriction (if applicable)	14	na	na	na	na	na	na	y	na	na	y	na	y	3	0	0	9
9	Allocation concealment	15	n	n	p	p	n	n	y	n	n	n	n	y	2	8	2	0
10	Who generated the allocation sequence?	16	n	n	n	n	y	n	y	n	n	n	n	y	3	9	0	0
10b	Who enrolled the patients?	17	n	n	n	y	y	n	y	n	n	n	n	y	4	8	0	0
10c	Who assigned the patents to the groups?	18	n	n	n	n	y	n	n	n	n	n	n	n	1	11	0	0
11	Blinding (were participants blinded?)	19	y	y	y	n	n	n	n	n	n	y	y	y	6	6	0	0
11b	Blinding (were the assessors blinded?)	20	n	n	y	p	n	n	y	n	n	n	n	y	3	8	1	0
11c	Was success of blinding evaluated?	21	n	y	n	na	na	na	na	na	na	n	n	n	1	5	0	6
12	Statistical methods	22	y	p	y	y	n	y	y	y	y	y	y	y	10	1	1	0
Results																		
13	Participant flow	23	n	p	n	p	n	n	y	y	p	y	p	p	3	4	5	0
13b	Report of study violations (if applicable)	24	na	na	na	p	na	n	y	y	n	p	y	y	4	2	2	4
14	Recruitment	25	n	n	n	p	n	n	y	p	n	y	n	y	3	7	2	0
15	Demographic and clinical characteristics	26	y	y	p	y	n	y	y	y	p	y	y	y	9	1	2	0
16	No. of participants in each group?	27	p	y	y	y	y	y	y	y	y	y	y	y	11	0	1	0
16b	Was it intention-to-treat analysis?	28	n	y	n	n	n	n	y	y	y	y	n	n	5	7	0	0
17	Effect size for each group for each outcome measure	29	p	p	y	p	y	y	y	y	p	p	p	y	6	0	6	0
17b	Precision of the effect size	30	n	p	p	p	p	n	y	p	p	p	p	p	1	2	9	0
18	If applicable, ancillary analysis stated in protocol?	31	na	na	na	na	na	na	na	na	na	y	na	p	1	0	1	10
19	Adverse events (if applicable)	32	na	na	na	na	na	na	n	na	n	n	n	n	0	5	0	7
Discussion																		
20	Discussion/interpretation	33	p	y	y	y	y	y	p	y	n	y	p	y	8	1	3	0
21	Generalizability	34	p	y	y	y	y	n	y	y	n	y	p	y	8	2	2	0
22	Overall evidence	35	n	p	n	y	p	y	y	n	n	y	n	p	4	5	3	0
	Sum														**191**	**118**	**61**	**50**
	Percent of applicable CONSORT criteria ($n = 370$)														52%	32%	16%	

*Mauro MT. The effect of Reiki therapy on maternal anxiety associated with amniocentesis. Masters thesis. University of Alberta, School of Nursing, 2001.

NA, not applicable.

in interpretation in what constituted partial (p) versus full (y) rating for the CONSORT analysis. After consensus discussions, the remaining disagreements (1%) were resolved by a third researcher (S.N.W.).

The 12 trials that studied a Reiki intervention in either a randomized controlled fashion or as a test versus control experiment are presented in Table 3. Eight (8) of the 12 studies identified themselves as RCTs. However, upon analysis of each of the study's text, the researchers were only able to identify 5 of the 12 (42%) publications as true RCTs.[20–24] Individual total applicable CONSORT criteria varied by study (see Table 2 for an individualized reporting of each criterion and Table 3 for a summary of adequately reported criteria by study).

Fifteen percent (15%) of the CONSORT Criteria items were not applicable for many of the trials (e.g., interim analyses,

Table 3. Study Type, Interventions, Outcomes, and Reporting Quality Based on a Modified CONSORT-Based Checklist

Study ref. no.	*Type of trial*[a]	*Comparison of intervention (whether Reiki ...)*	*Outcome measure*	*Adequately reported applicable criteria*
17	Test/control	Produces changes in autonomic nervous system	Heart rate (HR), blood pressure (BP), cardiac vagal tone (CVT), cardiac sensitivity to baroreflex (CSB) and respiratory rate (RR)	10/30 (33%)
25	Test/control	Aids in the recovery and rehabilitation in patients with subacute stroke	Functional Independence Measure and Depression (FIM), Center for Epidemiological Studies–Depression Scale (CES-D)	17/30 (57%)
23	RCT	Reduces depression and stress	Beck Depression Inventory (BDI), Beck Hopelessness Scale (HS), Perceived Stress Scale (PSS)	15/30 (50%)
21	RCT	Reduces pain and improved quality of life in patients with cancer	Visual Analogue Scale (VAS), Analgesic Use, BP, RR, HR	15/30 (50%)
22	RCT	Reduces pain and anxiety in women with hysterectomies	State–Trait Anxiety Inventory (STAI), VAS	15/28 (54%)
19	Test/control	Changes the isoprenoid pathway in seizure patients	Hepatic hydroxymethyl glutaryl Co-A reductase activity, serum digoxin level	12/29 (41%)
20	RCT	Reduces anxiety and depression in women undergoing breast biopsy	STAI, CES-D, Hospital Anxiety–Depression Scale (HADS)	27/32 (84%)
26	Pilot crossover	Reduces cancer-related fatigue in patients with cancer	Edmonton System Assessment System (ESAS); Functional Assessment of Cancer Therapy–General (FACT-G)–Fatigue (FACT-F)	19/30 (63%)
27	Test/control	Improves memory and behavior deficiencies in patients with Alzheimer disease	Annotated Mini-Mental State Examination (AMMSE) and Revised Memory and Behavior Problems Checklist (RMBPC)	10/31 (32%)
24	RCT	Reduces pain, anxiety, and depression in chronically ill patients	General Information Questionnaire; Social Readjustment Rating Scale; McGill Pain Questionnaire; BDI II; STAI; Rotter I-E Scale; Rosenberg Self-Esteem Scale; Belief in Personal Control Scale	20/34 (59%)
18	Test/control	Reduces pain and improves mobility in patient with painful diabetic neuropathy	McGill Pain Questionnaire; 6-minute walk test; Epidemiology of Diabetes Intervention and Complications Quality of Life Questionnaire; Well Being Questionnaire; Diabetes Treatment Satisfaction Questionnaire	10/32 (31%)
*	Pilot (test/control)	Reduces anxiety level of women undergoing their first amniocentesis	Sheehan Patient-Related Anxiety Scale (SPRAS) and Subjective Unit of Disturbance Scale (SUDS)	24/34 (71%)
	Total			194/370 (52%)

[a]As determined by researchers after reviewing the study.

*Mauro MT. The effect of Reiki therapy on maternal anxiety associated with amniocentesis. 2001. Masters Thesis. University of Alberta, School of Nursing.

randomization restrictions, ancillary analyses, blinding of practitioner). Items that were not applicable were not included in the calculations. For the group of 12 studies evaluated in the 35 item modified CONSORT checklist, over half of all items (52%) were reported adequately (Table 2). The remaining items were either not reported at all (32%) or reported partially (16%).

As a group, the 12 studies reported adequately the Introduction, the beginning part of the Methods section (CONSORT items 3–10), and most of the Results. Other than this, all the other sections were reported less than adequately: Methods—randomization, concealment and blinding (CONSORT items 11–22: 39% of items reported adequately); Results (specifically Intention-to-Treat: 42% adequately reported and Recruitment Dates: 25% adequately reported); and the Discussion section (56% of items reported adequately).

Individual studies ranged from 31% to 84% in adequately reporting applicable criteria. Assessment scores for all CONSORT criteria in the 12 trials are shown in Table 3.

Items reported adequately

The 12 trials adequately reported issues that are defined in the Introduction and beginning of Methods (all Methods except for Randomization, Assignment, and Blinding). These include: Reiki historical context with supporting literature, problem definition, study objectives, participant eligibility, description of participants and control subjects, dosage regimen for intervention and differences from control group treatment, and quality enhancements undertaken to improve outcome measurement. Over half the studies gave details about the practitioner performing the intervention.

Select criteria from the Results and Comments section were also adequately reported. These included: demographic and clinical characteristics of the groups, discussion, and generalization of the results. The number of patients in each group was almost always explicitly stated. The majority of studies reported mean scores and *p*-values, but less than half reported confidence intervals. The CONSORT criteria explicitly state that reporting *p*-values alone is not sufficient. Researchers must report confidence intervals so that readers can easily discern the overlap between mean scores.

Items seldom reported adequately

We identified major shortcomings in the reporting of the items displayed in the latter part of the Methods section (i.e., reporting the Randomization, Assignment, and Blinding). Only four trials[20–22,*] adequately detailed the randomization process. Of those four trials, only two trials[20,*] described the concealment of the allocation. For allocation concealment, we assumed that when no data were present, allocation was not concealed. A distinction was made between the two trials[20,*] where allocation was clearly concealed and those where there is some mention of concealment, but it is unclear whether this was achieved adequately.

Other examples of inadequate reporting: three trials[20,22,*] detailed who generated the allocation sequence and only one trial[22] specified who assigned the patients to their groups. Six trials[17,18,23,24,25,*] implemented blinding procedures for participants, but only one of them measured the success of the blinding.[25] Three (3) trials[20,21,23] mention blinding assessors. One trial (25) provided extensive background on the process and success of therapist blinding (for Reiki Level I practitioners) but only stated "patients were blinded" for the participant description. The CONSORT clearly states that this sentence is not enough to ensure that adequate blinding was achieved. The researchers rated this criterion for this trial as partially (p) adequately reported. In the other trials, masking of the participants or the therapists was not achieved due to a lack of a placebo arm (only a test and a control group).

Eight (8) trials identified specific primary outcome measures, but of these trials only four studies[20,21,25,26] provided a full rationale for sample-size calculation. On the basis of the reported numbers in the whole participant flow, we inferred that an intention-to-treat analysis was present in 5 of the trials.[20,24,25–27] Three (3) trials[21,24,*] mentioned the date range of the patient recruitment.

*Mauro MT. The effect of reiki therapy on maternal anxiety associated with amniocentesis. 2001. Masters Thesis. University of Alberta, School of Nursing.

Table 4. Jadad Scores

	Study reference no.											
Item no.	*17*	*25*	*23*	*21*	*22*	*19*	*20*	*26*	*27*	*24*	*18*	*
1	1	0	1	0	0	0	1	1	1	1	1	1
2	0	0	0	1	1	0	1	0	0	0	0	1
3	0	1	0	0	0	0	0	0	0	0	0	0
4	0	1	1	0	0	0	0	0	0	0	0	0
5	0	1	0	1	0	0	1	1	1	0	1	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	−1	0	0	0	0	0	0	0	0	0	0
Total	1	2	2	2	1	0	3	2	2	1	2	2

Score interpretation:
0–2 poor.
3–4 good.
5+ excellent.
*Mauro MT. The effect of Reiki therapy on maternal anxiety associated with amniocentesis. Masters thesis. University of Alberta, School of Nursing, 2001.

Jadad methodological quality: Findings

Based on the Jadad scores, 11 of the 12 studies were rated as methodologically "poor" with one study (20) rated as good. No studies were rated as "excellent" (Table 4).

Study results linked to level and experience of Reiki practitioner

Of the 128 studies evaluated, 9 stated significant positive findings on at least one outcome measure (not necessarily the primary outcome, as this often was not stated), while the other 3 studies[18,20,25] showed no significant outcomes (Table 5).

Of the three studies that showed no significant effect of Reiki, one[25] utilized a Reiki Master and 14 Level I Reiki practitioners; one used multiple Reiki Masters[18] and the other study[20] utilized 6 Level I or II Reiki practitioners. Of the 9 studies that showed a significant positive Reiki effect, 8 used a Reiki Master (or a Level II Reiki practitioner with more than 3 years experience). For the remaining study,[19] the researchers were not successful in their attempts to contact the author to determine the information (i.e., level of training or years of experience of the Reiki practitioner). As far as we could tell, no significant positive findings were found with Level I or II Reiki practitioners with less than 3 years of experience.

Discussion

Reiki use by patients in North America is growing; however, as shown by our analysis, this trend is not supported by adequate scientific data. There are few studies available to evaluate the efficacy of Reiki. Moreover, the few studies that are available are almost invariably of poor quality. Our analysis shows that the most important aspects that determine study quality (randomization, blinding, and accountability of all patients) are not well reported, nor is

Table 5. Summary of Studies

Ref. no.	Year	Authors	Journal	Study hypothesis	Population and study type	Outcomes	Conclusions
17	2004	Mackay N, Hansen S, McFarlane O	*Journal of Alternative and Complementary Medicine*	Reiki influences the autonomic nervous system.	$n = 45$; 24 females, 21 males, aged 23–59 years. Test vs. control.	Diastolic blood pressure response ($p < 0.005$) and heart rate changes ($p < 0.005$) were significantly different between Reiki and placebo.	Reiki has some effect on the autonomic nervous system.
23	2004	Goldman Shore A	*Alternative Therapies in Health and Medicine*	Reiki reduces psychologic depression and self-perceived stress.	$n = 45$, age 19–78. All in need of treatment for symptoms of depression and stress. Randomized controlled trial (RCT).	Significant difference on the Perceived Stress Scale (PSS) between Test 1(hands-on Reiki) and control (placebo group) ($p > 0.01$; $\eta^2 = 0.18$) and between Test 2 (remote Reiki) and placebo group ($p < 0.01$; $\eta^2 = 0.17$). No significant difference between two treatment groups. Similar results (Test 1 vs control; Test 2 vs control) on the Beck Depressive Index ($p = 0.05$; $\eta^2 = 0.9$ and $p = 0.004$; $\eta^2 = 0.18$ respectively) and the Hopelessness Scale ($p = 0.02$; $\eta^2 = 0.12$ and $p = 0.01$; $\eta^2 = 0.14$, respectively). No significant difference between types of treatment (hands-on vs. remote). One (1) year after the treatment, the difference maintained ($p < 0.05$; η^2 ranged from 0.12–0.44)	Hands-on Reiki and remote Reiki can reduce symptoms of depression, hopelessness, and stress. No significant difference between hands-on and remote reiki. The results were not due to placebo effects.
19	2003	Kumar R, Kurup P	*Neurology India*	Reiki-like treatments affect seizure patients.	n = 15, age 20–30 years. 8 males, 7 females. All with refractory seizure disorder.	The average seizure frequency decreased after treatment (2 per month in stead of 9 per month; $p < 0.01$). Increase in red blood cell membrane Na^+-K^+ ATPase activity ($p < 0.01$), serum magnesium ($p < 0.01$), and a reduction in hepatic hydroxymethyl glutaryl coenzyme A reductase activity ($p < 0.01$) and digoxin synthesis ($p < 0.01$), post-therapy.	Reiki-like treatment practices and transcendental meditation influence seizure frequency, biochemical pathways related to membrane Na^+-K^+ ATPase stimulation, and changes in neuronal transmission.
					Test vs control: 1 control group randomly chosen from the general population of Trivandrum city.	The concentration of serum tryptophan ($p < 0.01$), quinolinic acid ($p < 0.01$), and serotonin ($p < 0.01$) were reduced, post-therapy. The concentration of tyrosine ($p < 0.01$), dopamine ($p < 0.01$), and noradrenaline ($p < 0.01$) were increased, post-therapy.	

25	2002	Shiflett S, Nayak S, Bid C, Miles P	*Journal of Alternative and Complementary Medicine*	1. Reiki influences the functional recovery of patients with subacute stroke. 2. A procedure exists to blind both Reiki and sham Reiki practitioners.	$n = 50$, with subacute ischemic stroke. 31 male, 19 female. Test vs. control.	The effect on the Functional Independence Measure was not significant for the treatment group ($p > 0.50$). The Reiki practitioners were less confident than the non-Reiki practitioners about knowing in which group they were initiated ($p < 0.06$). Compared to Reiki practitioners, sham Reiki practitioners reported a greater frequency of feeling heat in the hands ($p < 0.03$).	1. Reiki had little or no effect on the functional recovery. 2. Reiki practitioners and sham practitioners did not differ in experience or sensations.
22	2006	Vitale AT, O'Conner PC	*Holistic Nursing Practice*	Reiki has a role as a therapy for pain management.	$n = 22$ women with scheduled abdominal hysterectomy. RCT.	At 24 hours after surgery, reports of pain were 3.8 for the experimental and 5.4 for the control group ($t = 1.79$; $p = 0.04$). No difference in reports of pain at 48 and 72 hours post-surgery.	Reiki influences postoperative pain for at least 24 hours.
21	2003	Olson K, Hanson J, Michaud M	*Journal of Pain and Symptom Management*	Reiki results in better pain control, less analgesic use, and an improved quality of life.	$n = 24$, 9 men (average age 59.5 years) and 15 women (average age 56 years), currently receiving palliative care due to advanced cancer. RCT.	A significant drop in pain in the standard opioid plus Reiki group on days 1 and 4 ($p = 0.035$; $p = 0.002$, respectively). Also a significant drop in diastolic blood pressure ($p = 0.035$; $p = 0.082$, respectively) and pulse ($p = 0.019$, only day 1).Quality of life significantly improved from days 1 to 7 for the standard opioid plus Reiki group ($p = 0.002$). No difference in analgesic use.	Reiki improved the quality of life and reduced the level of pain, but showed no difference in analgesic use.
20	2007	Potter P	*Journal of Holistic Nursing*	Reiki reduces psychologic stress in women undergoing breast biopsy.	$n = 35$ women scheduled for breast biopsy. RCT.	No significant difference in any of the 3 psychologic distress measures (State–Trait Anxiety Inventory [STAI], Center for Epidemiological Studies–Depression Scale [CES-D], Hospital Anxiety–Depression Scale [HADS]). Neither test nor control group showed pretest signs of depression or anxiety.	Reiki had no significant impact. Usual coping mechanisms were sufficient.

(continued)

Table 5. (Continued)

Ref. no.	Year	Authors	Journal	Study hypothesis	Population and study type	Outcomes	Conclusions
26	2007	Tsang KL, Carlson LE, Olson K	*Integrative Cancer Therapies*	Reiki reduces pain, fatigue, and anxiety and increases quality of life in patients with cancer. Reiki effect lasts for about 3 days.	$n = 16$ with various forms of cancer; (women = 13; men = 3); 12 white, 2 Asian, 2 Other; aged 33–84 (median age of 59 years).	Significant reduction between pretreatment and post-seventh treatment Reiki on fatigue ($p < 0.01$), pain ($p < 0.05$), and anxiety ($p < 0.05$). In comparison, there was no significant difference in the rest condition. Quality of life: Reiki condition reported a significant improvement in Functional Assessment of Cancer Therapy–General (FACT-G) pretest to post-test intervention ($p < 0.01$). No significant change in control condition.	Reiki was effective in decreasing fatigue, pain, and anxiety in patients with cancer. Overall quality of life improved compared to resting condition.
					Counter-balanced crossover trial where each individual participated in both conditions (Reiki and rest) but in random order.	Washout period: After careful monitoring, found that Reiki effect lasted for 7 days as fatigue scores did not drop.	Reiki benefited fatigued patients with cancer for at least 7 days.
18	2007	Gillespie E, Gillespie B, Stevens M	*Diabetes Care*	Reiki reduces pain in patients with diabetic nephropathy.	$n = 207$ with type 2 painful diabetic nephropathy (PDN); test vs. control with 3 groups: Reiki ($n = 93$); mimic Reiki ($n = 88$); Usual Care ($n = 26$). Usual Care was discontinued after randomization of 26 patients due to poor retention.	Significant reduction ($p < 0.05$) between baseline pain scores (McGill Pain Score) and 12-week pain scores for Reiki and mimic-Reiki groups. No significant reduction for Usual Care group. No significant reduction among final pain scores for all 3 groups (Usual Care group started with lower pain scores). Walking distance improved significantly ($p < 0.05$) for Reiki and mimic-Reiki groups; not for Usual Care group. All other measures (Visual Analogue Scale pain score; Well-Being Questionnaire; Diabetes Treatment Satisfaction Questionnaire) showed no significant difference.	Reiki was no more effective than mimic-Reiki in decreasing perceived pain and improving walking distance in patients with PDN.

24	1998	Dressen L, Singg S	*Subtle Energies and Energy Medicine Journal*	Reiki reduces pain, anxiety, and depression in chronically ill patients.	$n = 120$ who have been in pain for at least 1 year; RCT with 4 groups: Reiki, Progressive Muscle Relaxation; mimic-Reiki, and no treatment	Reiki proved significantly superior ($p < 0.001$–0.04) to other treatments on 10 of 12 variables measured. McGill Pain Score: Global Pain Intensity ($p < 0.001$); Sensory Pain Rating Index (PRI) ($p < 0.03$); Evaluative PRI ($p < 0.001$); Beck Depressive II Inventory ($p < 0.0001$); State–Trait Anxiety Inventory (State Anxiety, $p < 0.0001$), (Trait Anxiety, $p < 0.001$); Rosenberg Self-Esteem Scale ($p < 0.002$); Rotter Internal–External Locus of control ($p < 0.002$); Belief in Personal Control Scale (BIPCS) ($p < 0.01$); BIPCS-Scale C (Belief in God) ($p < 0.04$).	Reiki is an effective modality for reducing pain, depression, and anxiety. Reiki is effective in enhancing desirable changes in personality (self-esteem, locus of control). Reiki enhances one's faith in God. The effects of Reiki are not due to placebo.
27	2006	Crawford S, Leaver W, Mahoney S	*Journal of Alternative and Complementary Medicine*	Reiki results in improved memory and behavior deficiencies in patients with mild Alzheimer (MA)	$n = 24$ who scored between 20 and 24 on Annotated Mini-Mental State Examination (AMMSE); Test vs control with 2 groups: Reiki and no treatment	Reiki group showed significant ($p < 0.05$) AMMSE post-treatment scores (improved memory) over control; Reiki post-test scores in the Revised Memory and Behavior Problems Checklist (RMBPC) were significantly ($p < 0.05$) improved in both frequency and reactions over pretest and control group scores. Reiki group showed significant ($p < 0.05$–0.01) changes in memory-related and behavior-related questions.	Results indicate statistically significant ($p < 0.05$) increases in mental function (AMMSE) and memory and behavior problems (RMBPC) after Reiki treatment.
*	2001	Mauro MT	University of Alberta, Master's thesis	Reiki reduces a pregnant woman's anxiety level for amniocentesis.	$n = 30$ who were >35 years of age and between 15 and 18 weeks pregnant undergoing 1st amniocentesis; Test ($n = 10$), control ($n = 10$), and placebo ($n = 10$)	Anxiety scores were determined using Sheehan Patient-Related Anxiety Scale (SPRAS) and Subjective Unit of Disturbance Scale (SUDS). SUDS scores were obtained seven times (once before and six times after amniocentesis). Reiki and Placebo groups showed significant ($p = 0.013$) reduction in anxiety over control group as measured by SUDS. Significance between Reiki and Placebo could not be established due to low sample size.	Tentative positive results supports a larger study.

*Mauro MT. The effect of Reiki therapy on maternal anxiety associated with amniocentesis. Masters thesis. University of Alberta, School of Nursing, 2001.

their absence discussed in any of the Reiki studies, a fact that greatly diminishes the quality assessment of these trials.

We were only able to uncover 12 studies on which to perform our evaluation; these 12 studies had 31 different outcomes. This clearly shows that Reiki researchers are in "exploratory mode" in terms of understanding the benefits of Reiki. Although most of the outcomes indicated a positive outcome, it is quite possible that bias against the null hypothesis and the "file drawer syndrome" resulted in an unknown number of negative trials on Reiki never being published.[28] Hence, to further evaluate the validity of claimed therapeutic effects of Reiki, trials are needed with larger study populations and better reporting quality. It is obvious that these trials should be registered with a clinical trials register to avoid publication bias. In contrast, some researchers might argue that such studies should not be performed at all, since the biological substrate for Reiki's effect is unknown and plausible at best. However, while it may be difficult to scientifically assess Reiki's method of action with our current technology, it is possible to determine Reiki's efficacy. Given the increase in patient spending in CAM, we believe it is our job as researchers to conduct good quality trials which add to or refute the efficacy data of a given therapy.

Western medicine operates under the paradigm of evidence-based medicine. RCTs are considered the "gold standard" for providing evidence on effectiveness of biomedical interventions.[29] While Reiki itself is not a biomedical intervention, its efficacy needs to be proven, in service of good science. Current literature has suggested that RCTs alone may be limited in their ability to measure "whole person" healing, which is characteristic of CAM therapies (such as Reiki).[11] Adequate standards of reporting are necessary so that readers can make assessments on the internal and external validity of the trial as well as properly assess the results. The CONSORT statement was developed to aid authors in adequately reporting (and hopefully designing) their studies. In general, current reporting of trials is not considered adequate. In a study that looked at 253 RCTs reported in 5 leading medical journals (which have actively embraced the CONSORT) between 2002 and 2003, less than 60% of the trials adequately reported on allocation concealment (48%), randomization implementation (55%), blinding status of participants (40%), blinding of health care providers (17%), and blinding of outcome assessors (47%).[30]

Our findings are in agreement with an earlier observation that reporting of CAM trials is also poor.[31] In a project that assessed a sample of 206 RCTs of herbal medicine interventions, less than one third adequately reported whether those administering the intervention were blinded (28%), the methods for implementation (22%), and generation of the random allocation sequence (21%), whether there were protocol deviations (18%) or whether outcome assessors were blinded (14%).[29]

Biofield Energy Therapies are controversial to conventional health care providers and policymakers for two main reasons: (1) the dearth of rigorous scientific data that support or refute their efficacy, and (2) because biofields currently cannot be measured, so their scientific method of action remains questionable. While the second point may take more time to resolve, the first point can be addressed immediately, through adequate scientific reporting. In order for efficacy to be scientifically recognized, adequate reporting is required to inform readers of the purposeful deviations from traditional RCT design so readers can judge the influence of methodological flaws on the results of trials. In order to be accepted as true scientific evidence, adequate reporting of future Reiki RCTs or mixed methods RCTs is crucial. Of the items that were not reported adequately, all of them were reported adequately in at least one study, indicating that it is possible to report adequately.

A potentially significant finding from this study is that the level of training and/or years of experience of the Reiki practitioner seemed to be important for Reiki to be effective. A finding from the *Efficacy of Distant Healing* suggests that healers should have at least 3 years of practice to be considered performing optimally.[32] While the author of this study was not specifically referring to Reiki practitioners, it does make sense that a certain level of expertise improves the Reiki practitioners' efficacy.

We exempted Reiki Masters from the "3 years of practice" criteria that we applied to Reiki Practitioners (Level I and Level II) due to the intensive training that it takes to become a Reiki Master. Level II training is usually only given after a student has been practicing Level I Reiki for at least 3 months, though this can vary somewhat depending on the individual. Reiki Master training is primarily intended for people who have made Reiki their life's work. Depending upon the individual, Reiki Master level training is usually given only after a student has been practicing Level II Reiki for at least 1 year and the training is quite intensive.[9]

Studies that used Reiki practitioners (Level I or II) with less than 3 years experience showed no significant outcome, while in all but one of the studies that used a Reiki Master, there was a significant difference in measured outcome in the Reiki group. The goal of Reiki is to direct healing energy into the recipient. It has been suggested that the number of changes of Extra-Low Frequency (ELF) Magnetic Fields coming from Reiki practitioners' (i.e. Level I or Level II; non-Reiki Masters) hands differs significantly than the number of changes of ELFs coming from Reiki Masters' hands; however, the results of these studies have only been published in abstract and book form.[33] Although this is not a definitive test for efficacy of Reiki healers (no known test exists as far as we know), this does suggest that there is a difference between Reiki Masters and non-Master Reiki practitioners.

Conclusions

In order for Reiki studies to be evaluated and accepted based on their stated outcomes, authors need to ensure that the methodological quality and reporting of the study are adequate. This will only be achieved when authors are educated and disciplined in their approach to designing, executing, and reporting their studies. Alternative therapy journals should also actively embrace the CONSORT criteria to ensure that CAM therapies are reported at the highest scientifically accepted level. To date, based on the poor quality of studies and their reporting, it is currently impossible to draw definitive conclusions about the efficacy of Reiki.

Disclosure Statement

The authors state that no competing financial interests exist.

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The effect of distant reiki on pain in women after elective Caesarean section: a double-blinded randomised controlled trial

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ABSTRACT

Introduction: Approximately 25% of all babies in North America are delivered via Caesarean section (C-section). Though a common surgical procedure, C-section recovery can be painful. Opioids, specifically codeine, are commonly used to ease pain; however, its active metabolite, morphine, passes into breast milk, and may produce unwanted side effects in neonates; therefore, alternatives to opioids are being sought. Reiki is an ancient Japanese form of healing where practitioners transfer healing energy through light touch and positive healing intention. Although 1.2 million Americans use reiki to reduce pain or depression, there is a lack of strong evidence supporting its effectiveness. A recent systematic review showed existing studies to be of poor methodological quality, with the common limitation of lack of blinding. To overcome this issue, the authors used distant reiki to assess its effectiveness in reducing pain following an elective C-section.

Methods: In this randomised, double-blinded study, women who underwent an elective C-section were allocated to either usual care (control, n=40) or three distant reiki sessions in addition to usual care (n=40). Pain was assessed using a visual analogue scale (VAS). The primary endpoint was the Area Under the VAS-Time Curve (AUC) for days 1–3. Secondary measures included: the proportion of women who required opioid medications and dose consumed, rate of healing and vital signs.

Results: AUC for pain was not significantly different in the distant reiki and control groups (mean±SD; 212.1±104.7 vs 223.1±117.8; p=0.96). There were no significant differences in opioid consumption or rate of healing; however, the distant reiki group had a significantly lower heart rate (74.3±8.1 bpm vs 79.8±7.9 bpm, p=0.003) and blood pressure (106.4±9.7 mm Hg vs 111.9±11.0 mm Hg, p=0.02) post surgery.

Conclusion: Distant reiki had no significant effect on pain following an elective C-section.

Clinical Trial Registration Number: ISRCTN79265996.

ARTICLE SUMMARY

Article focus

- This is the first randomised, double-blinded trial conducted on distant reiki.
- The focus in on distant reiki's effects on pain after Caesarean section.
- Special attention was paid to the methods of proper randomisation, patient allocation concealment and blinding.

Key messages

- Our trial suggests that distant reiki had no benefit in reducing patients' postpartum pain over usual care for elective Caesarean section.

Strengths and limitations of this study

- We engaged a highly experienced reiki master to administer distant reiki removing the placebo effect which was present in all other pain trials. In addition, we maintained a high adherence to protocol, successful blinding of the research team, successful randomisation and patient allocation concealment, and diligent data collection with extremely few data points missed. We had good credibility with research participants, as all but 10 women refused to participate. We evaluated other aspects of healing after elective Caesarean section, beyond patients' perceived pain levels, by including the previously developed and published Milestone Questionnaire.
- A potential limitation was the magnitude of pain on which we were attempting to show an impact. Just as acetaminophen is not suitable as pain medication after Caesarean section, distant reiki may also not be suitable for this magnitude of pain. In addition, since some patients were discharged early, our complete dataset is limited to 48 h, with gaps in data for 16 patients (20%) accounted for by carrying the last pain score forward. To ensure that this method did not distort the results, we also evaluated AUC for pain on day 1 and day 2 individually and found no differences between groups for both these time periods.

INTRODUCTION

Approximately 25% of all babies in North America are delivered via Caesarean section (C-section)[1]; alleviating pain early is important, as studies have shown that postoperative pain negatively affects a mother's ability to care for and breastfeed her infant.[2] To alleviate postoperative pain, opioids are commonly used after C-section.[3] For example, codeine, a common opioid, is a prodrug, and it is the relative biotransformation of codeine into morphine by the highly polymorphic cytochrome P450 enzyme 2D6 (CYP2D6) that is the single most important factor determining codeine analgesia in adults. Approximately 5–10% of ingested codeine is converted into morphine; however, this percentage can increase dramatically in individuals who have multiple copies of the CYP2D6 allele.[4]

We now know that morphine passes into breast milk. In 2005, a published study alerted the medical community to a case where a full-term breast-fed baby died from a morphine overdose as a result of his mother taking Tylenol no 3 with codeine to manage her pain; the mother had several copies of the CYP2D6 allele and had converted more than 10% of codeine into morphine.[5 6] Maternal breast milk is considered the optimal nutrition for infants, and the American Academy of Pediatrics recommends exclusive breastfeeding for the first 6 months of life.[7] To ensure that all mothers who are recovering from C-sections and wish to breastfeed are able to do so safely, alternatives to opioids are sought.

Several complementary and alternative medicine therapies are used to alleviate pain. In an attempt to reduce or eliminate the need for opioid pain medication, we sought to examine the effect of distant reiki on pain. Reiki, an ancient Japanese form of hands-on healing, used to alleviate pain and depression,[8] is classified as an Energy Medicine by the National Center for Complementary and Alternative Medicine (NCCAM).[9] Despite being an ancient Japanese practice, reiki is practised by over 1.5 million Americans, and its popularity is growing.[10] It was promoted by Dr Oz, prominent cardiothoracic surgeon, host of the Dr Oz Show and frequent Oprah guest, as his 'ultimate complementary and alternative medicine therapy for 2010.'[11] However, while it is commonly practised, there is no agreed-upon theory for how reiki might work, and its mechanism of action is still unknown.[8]

Reiki practitioners believe that they can direct healing energy through their hands to their patients. To direct this energy, practitioners maintain a meditative presence and place their hands lightly over the person they are treating to aid in the patient's natural ability to heal. Reiki can be practised either proximally, with the patient located beside the practitioner, or distally, with the patient and practitioner in separate locations. Both types of reiki rely on the premise of a universal source of healing energy which a reiki practitioner can direct through intention.

A distant reiki treatment is like distant prayer, in that the practitioners are thinking of their patients from a distance. In distant reiki, reiki practitioners first undertake a specific protocol which allows them to send the healing energy to the patient. Second, practitioners mentally ask the person who is absent if he or she consents to treatment. Lastly, if practitioners do not hear a response or if they hear 'yes' in their head, they follow the same procedure as for traditional reiki, but they place their hands on a substitute (eg, pillow) for the person being treated; if they hear 'no,' the session ends immediately.

Reiki may work. Several studies have found a reduction in pain when using reiki[12–15]; furthermore, one of the studies found that women who received reiki after hysterectomy reported less pain and requested fewer analgesics.[12] While there were no studies which specifically evaluated distant reiki for pain, one study found that distant reiki was as effective as traditional reiki in the management of depression and anxiety. The authors concluded that the distant reiki was as efficacious as traditional reiki, and the healing power of reiki was not due to placebo.[16]

However, despite widespread and growing popularity, there is a dearth of well-conducted published scientific literature supporting or refuting reiki's efficacy. A recent systematic review of reiki found that while the vast majority of studies had positive therapeutic effects, all available studies scored poorly when methodological quality was measured using Jadad[8]; thus, definitive conclusions about efficacy could not be made. A common source of potential bias was the lack of blinding of participants and assessors when using traditional reiki. Patient and medical-staff blinding to treatment allocation in a clinical trial is particularly important when the response criteria are subjective, such as alleviation of pain.[17] To overcome this limitation, we employed distant reiki in our trial.

Given the need for alternate pain-control treatments for breastfeeding mothers owing to the risk of morphine exposure in neonates, and the reduced pain observed in the women who received reiki after hysterectomy, our objective was to determine if distant reiki is effective in reducing pain after elective C-section, through a randomised double-blinded study.

METHODOLOGY

Study design

This was a double-blinded randomised clinical trial. The investigators, participants and healthcare staff directly involved with the participants were unaware of the group assignments. The study was approved by the research ethics board at St Michael's Hospital in Toronto, and all participants provided written informed consent prior to participation.

Participants

All pregnant women who were scheduled to have an elective C-section were approached during a routine prenatal visit at the obstetrical clinic at St Michael's

Hospital between 1 September 2008 and 31 March 2009. Criteria for exclusion included the following: having had previous experience with reiki or not planning to use standard postoperative pain medication. Women were recruited in either English or Spanish, and those who did speak other languages were approached if they had a translator with them, such as a husband or friend.

To ensure concealment of group assignment, the St Michael's Hospital research associate (SvdV) enrolled participants and then contacted the research assistant (YIG) at The Hospital for Sick Children with the participant's information (unique Hospital ID, date and time of C-section) for randomisation. YIG had previously generated the randomised number sequence in blocks of four or six. Participants were sequentially assigned (by YIG) to the random sequence, which was securely stored and password-protected on the Hospital for Sick Children network. If the patient was assigned to the distant reiki group, the research assistant (YIG) contacted the reiki master with the participant's information. If the patient was in the control group, no contact was made with the reiki master.

Intervention

Participants in the control group received usual medical and nursing care during their stay (typically 72 h). The intervention group received usual care plus three distant reiki sessions, one each morning. The first session was administered on the morning of the C-section, at least 30 min prior to surgery, and the second and third sessions were administered on the following mornings at approximately 08:00.

A single reiki master located over 100 km away, who was trained in the Usui line of reiki and has been practising reiki for over 10 years and regularly treats clients with distant reiki, administered the distant reiki interventions. Each distant reiki session lasted approximately 20 min, and the reiki master followed the traditional Usui reiki protocol for distant healing.[18] The unique Hospital ID was used as the identifier when sending distant reiki to the participant.

C-section, anaesthesia and analgesia protocol

All elective C-sections at St Michael's Hospital were performed using the Pfannenstiel protocol.[19] Women who underwent elective C-sections received spinal anaesthesia with 0.75% bupivicaine, and 15 µg of fentanyl lasting 2–4 h followed by 100 µg of epidurally administered morphine, which typically lasts 12 h. Vital signs were checked, and pain and sedation scores were taken every 10 min for 2 h after the C-section. Following these 2 h, vital signs were taken every 12 h on the delivery ward.

The following analgesia protocol was administered immediately following the C-section:

1. Naproxen (500 mg) was given rectally and then orally every 12 h for 48 h.
2. For breakthrough pain: acetaminophen (300 mg) with codeine (30 mg) and caffeine (15 mg) (Tylenol no 3, Johnson & Johnson, New Brunswick, New Jersey), 1–2 tabs orally, every 4 h, as needed.
   a. patients who could not tolerate acetaminophen with codeine were given either acetaminophen (325 mg) with oxycodone (5 mg) (Percocet, Endo Pharmaceuticals, Chadds Ford, Pennsylvania) or oral morphine (5 mg).
3. For mild to moderate pain: acetaminophen, 500 mg (Tylenol Extra Strength, Johnson & Johnson), 1–2 tabs orally, every 4 h, as needed.
4. Forty-eight hours after the C-section, the women received a self-medication package. This package included:
   a. acetaminophen, 325 mg (Tylenol, Johnson & Johnson), 1–2 tabs orally, every 4–6 h, as needed for mild pain control;
   b. ibuprofen, 200 mg (Advil, Wyeth Consumer Healthcare, Richmond, Virginia), 1–2 tabs orally, every 4–6 h, as needed for moderate pain control;
   c. docusate sodium, 100 mg (Colace, Purdue Pharma, Stamford, Connecticut), 1 capsule orally, twice a day, as needed for constipation;
   d. zinc sulfate monohydrate (0.5%) with hydrocortisone (0.5%) (Anusol HC Ointment, Pfizer Consumer Healthcare, Morris Plains, New Jersey) applied to the anal area for haemorrhoids, if applicable.
5. Upon discharge, women were also given a prescription for 300 mg of acetaminophen with 30 mg of codeine and 15 mg of caffeine, which they could complete at their local pharmacy if required.

Outcome measures

A research associate collected baseline ethnodemographic and pain-history data, while a nurse measured baseline vital signs prior to surgery and prior to first distant reiki treatment. All personal patient information was deidentified by a numeric code to protect patient confidentiality.

The primary endpoint for the study was the area under the curve (AUC) for pain (in movement) for days 1–3 using the visual analogue scale (VAS),[20 21] corresponding to a person's total pain. The VAS is a 10 cm line with an anchor at each end. Under the anchor on the left-hand side is '0: no pain,' and under the anchor on the right-hand side is '10: worst pain.' A research assistant collected two sets of pain scores three times each day (07:30–09:30; 12:00–14:30; and 17:30–20:00). The two sets of pain scores corresponded to the amount of pain felt at that moment in rest, and the amount of pain felt when moving. In addition, each morning, participants were asked to indicate the worst level of pain felt during the night.

Secondary endpoints included the following 10 measures: AUC for pain in motion for days 1, 2 and 3 separately; the mean VAS (in motion) from days 1–3; the mean VAS (in rest) from days 1–3; the number of patients in need of opioid pain medication; the dose of

codeine equivalent consumed per kilogram of body weight; the number of adverse events to opioids such as constipation or itchiness; mother's respiratory rate, heart rate and blood pressure (systolic and diastolic); and the time to first activity (first hunger, first spontaneous voiding, first eating solid foods, first walk, etc) using the Milestone Questionnaire. The Milestone Questionnaire was previously used on women post elective C-section to evaluate their rate of healing.[22] As reiki is used not only for pain, but also to send 'healing energy to where the body needs it most,'[23] this activity milestone questionnaire was used to capture additional healing that could have taken place.

Statistical analysis

Reporting adhered to the Consolidated Standards of Reporting Trials statement for reports of parallel-group randomised designs.[24] The Area Under the VAS-Time Curve was calculated by plotting the VAS scores on the timescale and dividing the curve into a series of trapezoids (figure 1). Opioid medications were converted to codeine equivalents (60 mg of oral codeine was considered equivalent to 10 mg of oral morphine and 6.7 mg of oxycodone).[25 26] All analyses were performed by intention to treat. We calculated that 40 participants per group would be required for the study to have 80% power to show a clinically significant 25% mean reduction in pain with distant reiki as compared with placebo. A 25% mean pain reduction was determined a priori to be clinically relevant by our expert clinicians, since the literature concludes that 20–33% reduction is considered clinically significant.[27–29] For power analysis, we used an SD in pain of 56% in the normal postoperative C-section population.[30] Baseline demographic and outcome variables were compared using the Student t test, Mann–Whitney U test or Fisher exact test where appropriate. For missing data, we used the last-observation-carried-forward method in the analysis of AUC and mean pain scores.

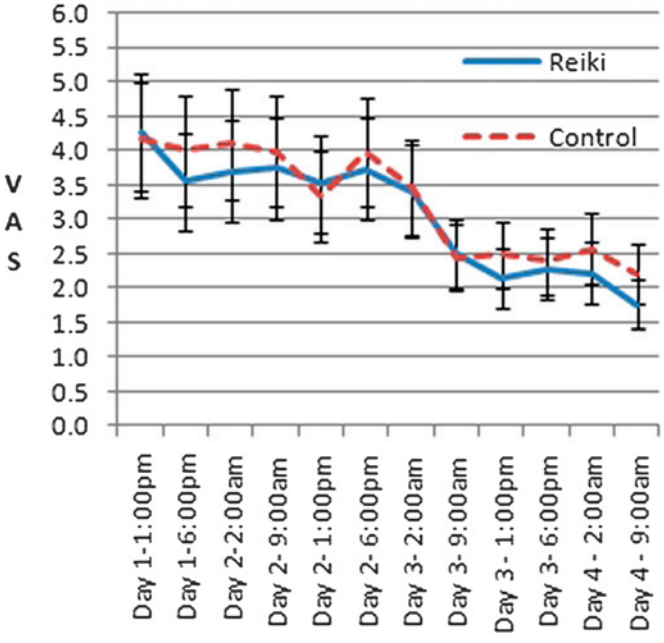

Figure 1 Visual analogue scores (VAS) for pain in movement after Caesarean section for women receiving distant reiki (Reiki) and usual care (control). Values are means (n=40)±SD.

RESULTS

One hundred and thirty women were eligible for participation in this study, 47 women were excluded (did not meet inclusion criteria, refused or did not speak English/Spanish), and 83 women were enrolled (figure 2). A total of 42 women were randomised to receive distant reiki, and 41 women were randomised into the control group. Three women were withdrawn from the study after randomisation: one woman (control group) was withdrawn, as she suffered a severe haemorrhage during surgery and remained in the ICU for several days, leaving researchers unable to collect her pain-score data; two participants were withdrawn from the distant reiki group, as they received general anaesthesia instead of spinal anaesthesia (thus, they no longer met inclusion criteria). This left a total of 40 women randomised into each group.

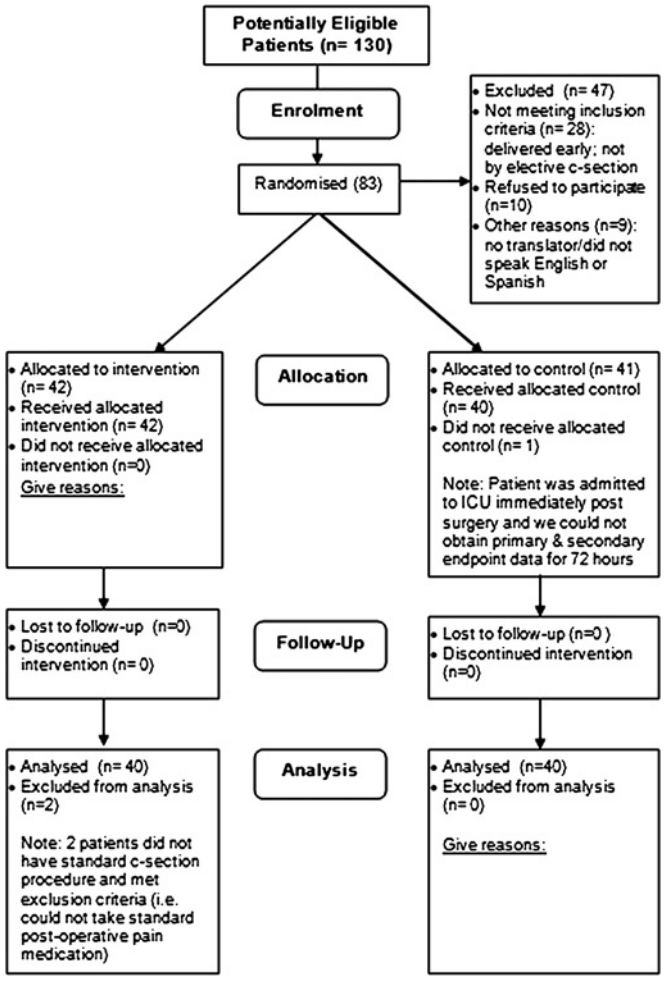

Figure 2 Patient recruitment and analysis: the Consolidated Standards of Reporting Trials E-flow chart.

Table 1 Demographic and baseline characteristics of the participants

Characteristics; no (%)	Reiki (n=40)	Control (n=40)	Difference mean (95% CI)	p Value
Maternal age (years)				
Mean±SD	35.1±5	32.9±6	2.2 (−0.3 to 4.7)	0.06
Range	21 to 44	19 to 44		
No of previous C-sections†				
Median	1	1	NA	0.90
Range	0 to 3	0 to 3		
Ethnicity*				
Caucasian	19 (47.5%)	16 (40%)	NA	0.51
Asian	12 (30%)	14 (35%)	NA	
Hispanic	3 (7.5%)	7 (17.5%)	NA	
Afro Carribbean	5 (12.5%)	3 (7.5%)	NA	
Other (Iranian)	1 (2.5%)	0	NA	
Self-reported pain-tolerance score: scale (1 to 10)				
Mean±SD	6.2±2.1	6.6±1.6	−0.4 (−1.2 to 0.4)	0.40
Range	1 to 10	2 to 10		
Weight of mother (kg)				
Mean±SD	83±12.6	79±15.5	4 (−2.3 to 10.3)	0.22
Range	54 to 111	54 to 145		
Previous pregnancies				
First-time pregnancy*	4 (10%)	6 (10%)		
>4 pregnancies*	3 (7.5%)	4 (10%)		
Mean±SD	2.8±1.2	2.6±1.2	0.2 (−0.3 to 0.7)	0.40
Range	1 to 6	1 to 6		
No of children living†				
Median	1	1	NA	0.94
Range	0 to 4	0 to 3		
Duration of Caesarean section surgery (min)				
Mean±SD	41.9±11.9	45.3±19.2	−34 (−10.5 to 3.7)	0.35
Range	23 to 70	28 to 146		
Baby Apgar scores (1 to 10)				
1 min (mean)±SD	8.7±0.6	8.7±0.7	0 (−0.3 to 0.3)	0.88
5 min (mean)±SD	9.1±0.5	9.3±0.5	−0.2 (−0.4 to 0)	0.15
Weight of newborn babies (g)				
Mean±SD	3579±469	3228±424	351 (152 to 550)	<0.001‡
Range	2745 to 5315	2625 to 4332		
No of babies over 4000 g	5 (12.5%)	4 (10%)		
Gestational age of babies (weeks)				
Mean±SD	38.5±0.7	38.3±0.6	0.2 (−0.1 to 0.5)	0.08
Range	37.5 to 40.5	37 to 39.5		

*p Values for comparisons of ethnicity and number of pregnancies was determined by Fisher exact test. All other comparisons were determined using an unpaired t test unless noted.
†Mann−Whitney U test for non-parametric data. Self-reported pain tolerance scores were taken before the C-section. A score of '1' was low pain tolerance, while a score of '10' was high pain tolerance.
‡Significance ($p<0.05$).
NA, not applicable to median or proportion calculations.

No patients mentally refused the distant reiki intervention, and the two groups did not differ significantly in baseline measures or demographic characteristics (table 1) except for birth weight of newborns ($p<0.001$); differences between groups in maternal age approached significance ($p=0.06$).

During days 1 and 2, a total of three pain scores, which represented less than 1% of the data, were not collected because the patients were sleeping during the time to record their level of pain; all other data for patients were captured (pain medication consumption, physiological measures and time to first activity) on these days. However, on day 3, a total of 16 patients (20%), eight from the distant reiki group and eight from the control group, were discharged early (after 48 h instead of after 72 h in hospital) resulting in 20% missing data (pain scores, pain medication consumption and time to first activity). AUC pain data were not compared between distant reiki and control groups for day 3 alone, owing to the large amount of missing data.

No significant difference was seen between groups in the primary outcome of overall pain from days 1−3. The mean (±SD) AUCs for pain for days 1−3 in the distant reiki and control group were 212±104 and 223±118 respectively ($p=0.96$). There were no significant differences between groups in AUC for pain for day 1 or day 2,

Table 2 Outcomes for days 1–3 (combined), day 1 and day 2

	Reiki group (n=40) Mean±SD†	Control group (n=40) Mean±SD†	Difference mean (95% CI)	Signficance§ p value
Area Under the Curve Pain Scores (in movement)*				
Days 1–3 combined	212.1±104.7	223.1±117.8	−11 (−60.6 to 38.6)	0.96
Day 1	74.2±39.6	79.7±42.9	−5.5 (−23.9 to 12.9)	0.55
Day 2	82.9±41.5	84.5±45.7	−1.6 (−21.0 to 17.8)	0.87
Mean pain scores (cm)				
Days 1–3 (in movement)	3.1±1.5	3.3±1.7	−0.2 (−0.9 to 0.5)	0.61
Days 1–3 (in rest) (median, IQR)†	1.1 (0.4 to 1.7)	1.4 (0.6 to 2.1)	NA	0.32* §
Pain medication consumption (mg of codeine equivalent/kg body weight¶)				
Day 1 (median, IQR)	0.7 (0 to 1.4)	1.1 (0 to 2.0)	NA	0.35* §
Day 2 (median, IQR)	0.5 (0 to 1.7)	0.6 (0 to 1.5)	NA	0.36* §
Days 1–3 (median, IQR)	1.7 (0 to 3.12)	1.7 (0 to 4.4)	NA	0.87* §
Patients on opioids: no (%)				
Day 1	24 (60)	26 (65)	NA	0.56** §
Day 2	23 (58)	21 (53)	NA	0.56** §
No of adverse events to codeine				
Day 1 (median, IQR)	0 (0 to 0)	0 (0 to 1)	NA	0.36* §
Day 2 (median, IQR)	0 (0 to 0)	0 (0 to 0)	NA	0.84* §
Activity milestone (h)				
Time to first hunger	15.5±18.9	10.9±13.0	4.6 (−2.6 to 11.8)	0.15* §
Time to first eating solid food	23.6±12.1	23.9±12.3	−0.3 (−5.7 to 5.1)	0.88
Time to first flatus	19.8±12.8	20.1±12.4	−0.3 (−5.9 to 5.3)	0.92
Time to first bowel movement	57.7±15.6	57.9±16.7	−0.2 (−7.4 to 7.0)	0.95
Time to first spontaneous voiding	17.0±5.5	17.7±5.0	−0.7 (−3.0 to 1.6)	0.60
Time to first ambulation	16.9±5.3	17.2±5.2	−0.3 (−2.6 to 2.0)	0.82
Heart rate (per minute)				
Baseline—prior to surgery	84.4±9.4	84.8±10.6	−0.4 (−4.9 to 4.1)	0.88
Day 1 (4 h post surgery)	74.3±8.1	79.8±7.9	−5.5 (−9.1 to −1.9)	0.003‡
Difference between baseline and day 1 (4 h post)	10±11.3	4.9±11.5	5.1 (0.1 to 10.2)	0.04‡
Day 1—20:00	79.0±7.8	79.6±7.7	−0.6 (−4.0 to 2.8)	0.72
Day 2—08:00	80.5±8.1	80.8±7.8	−0.3 (−3.8 to 3.2)	0.84
Day 2—20:00	81.3±7.0	80.8±6.1	0.5 (−2.4 to 3.4)	0.73
Day 3—08:00	76.5±8.7	77.6±8.0	−1.1 (−4.8 to 2.6)	0.54
Diastolic blood pressure (mm Hg)				
Baseline—prior to surgery	71.2±8.6	71.3±9.6	−0.1 (−4.2 to 4.0)	0.94
Day 1 (4 h post surgery)	66.9±8.2	67.3±8.2	−0.4 (−4.0 to 3.2)	0.82
Day 1—20:00	65.8±6.9	65.9±8.9	−0.1 (−3.6 to 3.4)	0.94
Day 2—08:00	64.5±7.2	65.8±8.3	−1.3 (−4.8 to 2.2)	0.43
Day 2—20:00	66.8±8.6	64.6±7.1	2.2 (−1.3 to 5.7)	0.21
Day 3—08:00	64.9±7.6	67.7±7.8	−2.8 (−6.2 to 0.6)	0.09
Systolic blood pressure (mm Hg)				
Baseline—prior to surgery	120.1±11.7	118.1±15.7	2 (−4.2 to 8.2)	0.52
Day 1 (4 h post surgery)	107.8±10.9	109.4±12.1	−1.6 (−6.7 to 3.5)	0.54
Day 1—20:00	107.8±9.7	107.3±12.9	0.5 (−4.6 to 5.6)	0.85
Day 2—08:00	104.0±10.3	106.9±10.3	−2.9 (−7.5 to 1.7)	0.21
Day 2—20:00	110.3±11.3	106.0±10.8	4.3 (−0.6 to 9.2)	0.08
Day 3—08:00	106.4±9.7	111.9±11.0	−5.5 (−10.1 to −0.9)	0.02‡
Difference: baseline to day 3 at 08:00	13.7±14.4	6.2±13.3	7.5 (1.3 to 13.7)	0.02‡

*Area Under the Curve pain scores were calculated by taking the trapezoidal area after measuring pain scores from the VAS 10.0 cm scale.
†Values are means±SD unless otherwise noted. Values were calculated based on 40 participants in each group.
‡Signficance defined as $p<0.05$.
§Significance tests measured using Student t test unless noted: Mann–Whitney test (*) or Fisher exact test (**).
¶Opioid conversion described in Methodology section.
NA, not applicable to median and IQR.

mean VAS pain scores (in rest or in motion), use of opioids, dose (mg/kg body weight) of opioid medication consumed or time to first activity (table 2). The main outcome and most secondary outcomes were normally distributed, with the notable exception of pain-medication consumption and adverse events which were not normally distributed.

To determine if the two variables which varied between the two groups (baby birth weight and mother's age) affected the primary outcome, we performed a multivariate regression analysis with three independent variables; mother's age, baby's birth weight and group allocation were regressed against the dependent variable: AUC of pain for days 1−3. Both baby's birth weight and mother's age were found to be significant (p=0.013, p=0.046 respectively), while the distant reiki group allocation was still not significant (p=0.558).

There was a small but significant difference in heart rate on day 1, 4 h after C-section (see figure 3 for timeline), whereby the mean (±SD) heart rate in the distant reiki group was 74.3±8.1 bpm compared with 79.8±7.9 bpm in the control group (p=0.003). Systolic blood pressure on day 3 at 08:00 was also significantly lower in the distant reiki group (106.4±9.7 mm Hg) compared with the control group (111.9±11.0 mm Hg) (p=0.02). Otherwise, there were no significant differences between groups in the physiological measures.

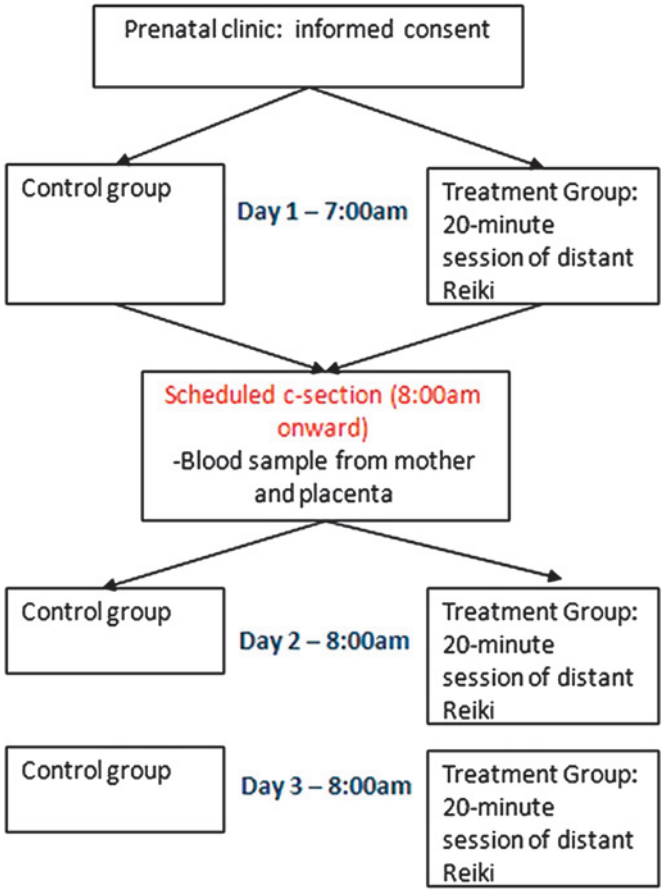

Figure 3 Timeline for surgery, first distant reiki treatment and vital measures time.

There were no significant differences in the rates of adverse events between the two groups.

DISCUSSION

This study measured perceived pain and healing in women over their 3 days in hospital, while they recovered from an elective C-section. We found no beneficial effect of distant reiki over usual care for pain reduction up to 3 days after elective C-section.

The lack of an observed benefit of distant reiki for all pain outcome measures at all points in time is in contrast to most,[12–15] but not all,[31] earlier reiki pain studies. However, unlike all earlier published studies, our study differed in two key regards: firstly, ours was the only randomised and double-blinded trial. In addition to the patients not knowing their group assignment, the investigators and outcome assessors were unaware of the intervention assignment. This suggests that the therapeutic benefit of reiki for pain observed in previous, non-blinded studies was a placebo effect or that the magnitude of pain from an elective C-section is too great for distant reiki to make an impact.

Secondly, we employed distant reiki, and not traditional hands-on reiki, as our intervention. In considering the physiological effects of reiki, one of the basic teachings of healing with reiki is that we are more than our physical bodies. We also have an energy body made up of our aura (energy fields), the chakras (energy centres) and the meridians (energy pathways). Because reiki healers believe that reiki energy is not limited by time and distance, distant reiki healings can also be given without the client being present.[18] Reiki practitioners assert that a distant reiki intervention works by directing healing energy which engages the body by generating biological reactions such as pain reduction.

It is well accepted that many constituents of living systems communicate with each other via electromagnetic signals. A number of studies have demonstrated that weak electromagnetic fields (EMF) are capable of eliciting in vivo and in vitro effects from different biological systems. Endogenous electromagnetic and magnetic fields are associated with many basic physiological processes, ranging from ion binding and molecular conformation in the cell membrane to the macroscopic mechanical properties of tissues.[32–41]

In an attempt to validate energy therapies such as reiki, researchers have been measuring classical electromagnetic (EM) fields emitted by the body using both physical[42–45] and biological[46] detectors. However, the intensity of these fields fades rapidly with distance, and thus cannot explain the effect of distant reiki.

One author[47] has proposed that in addition to classical EM fields, the body generates non-classical and quantum fields, which do not fade with distance. Several studies have shown that quantum fields can influence neurological[48] and immunological functions[49] at the cellular level. However, the idea that reiki energy works through quantum fields is highly controversial,

and more scientific trials need to be conducted in this area.

Another possible explanation for the lack of observed effect is the study's sample size. Based on our calculations, the distant reiki would have had needed to have an effect size of 0.55; however, based on the AUC for pain, distant reiki had an effect size of 0.1, which is considered to be very small. Using this effect size, a total of 2530 patients (1265 per group) would have been needed to see a significant difference between groups. It is unlikely that the failure to find significant differences is due to selection bias, as only 10 women (12.5%) refused to participate in the study.

The Milestone Questionnaire which recorded time to first activity also showed no differences between groups. We evaluated these responses against the measures obtained by Roseag and colleagues,[22] and found all rates of healing to be similar to their published results, except for time to first eating solid foods, where our study showed an average of 10 h longer for both groups. This could be due to the fact that St Michael's Hospital does not routinely allow women to eat solid foods until after they have passed gas, regardless of whether or not they are hungry.

Despite randomisation, there was a statistically significant difference between the two groups in birth weight; differences in maternal age approached significance. Our finding that a mother's perceived pain decreases with maternal age is consistent with previous studies.[50 51] However, we could not find any literature to support or refute the finding that larger babies born via elective C-section caused more pain. The increase in mothers' pain could be due to larger uteri which housed larger babies, thereby resulting in more pain as they contracted back to normal. In addition, lifting heavier babies post surgery could result in more pain for a recovering mother.

Heart rate taken approximately 4 h after C-section and systolic blood pressure taken on day 3 at 08:00 (table 2) were significantly lower in the distant reiki group compared with the control group. This is consistent with three studies,[13] two of which[52 53] specifically examined the physiological changes as a result of reiki. However, given that distant reiki's method of action is unknown, there is the possibility that our findings are simply due to chance, given the number of secondary measures evaluated. The small but statistically significant benefits of lower heart rate and blood-pressure levels are unlikely to be clinically significant but may be interesting to future researchers who are searching for a mechanism of action for distant reiki.

The generalisability of our study may be limited, given that one reiki master performed all of the distant reiki treatments; in addition, given the absence of information about the mechanism of action of distant reiki, we chose the same dosage that in a published trial using traditional reiki.[12] Outcomes may differ given other reiki practitioners and other dosage regimes.

CONCLUSION

In conclusion, our trial showed no significant benefit of distant reiki (administered once per day) over usual care for pain management in the first 3 days after elective C-section. It is not recommended as a method of primary pain relief for women undergoing an elective C-section.

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Competing interests SvdV is a reiki practitioner.

Ethics approval This study was approved by the Review Ethics Board (REB) at St Michael's Hospital in Toronto, Ontario.

Contributors SvdV and GK conceived the study. SvdV, HB, VMGJG, SNdW, AT and GK designed the study. SvdV, CT, YIG and VNGJG acquired the data. SvdV and GK analysed the data. SvdV drafted the article. All authors interpreted the data, revised the article critically for important intellectual content and approved the final version. GK had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

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The effect of distant reiki on pain in women after elective Caesarean section: a double-blinded randomised controlled trial

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Notes

CYP2D6 Polymorphisms and Codeine Analgesia in Postpartum Pain Management: A Pilot Study

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Background: Codeine, a common opiate prescribed for pain postcesarean section (c-section), is biotransformed by the highly polymorphic Cytochrome P450 enzyme 2D6 (*CYP2D6*). Ultrarapid metabolizers (UMs), individuals with multiple active copies of *CYP2D6*, can biotranform up to 50% more codeine into morphine than normal individuals can. In contrast, poor metabolizers (PMs), individuals who have no active *CYP2D6* genes, convert almost no codeine into morphine and as a result may take multiple doses of codeine without attaining analgesia.

Objective: The aim was to study the relationship between *CYP2D6* genotype and codeine analgesia among women recovering from c-section.

Methods: Forty-five mothers prescribed codeine provided a blood sample for *CYP2D6* genotyping and recorded their pain level 4 times a day for 3 days immediately after a c-section. Codeine was used on an as-needed basis; doses and times were recorded. The relationship between *CYP2D6* genotype, pain scores, need for codeine, and adverse events was studied. Theoretical morphine dose, based on *CYP2D6* genotype, was estimated.

Results: Women at the genotypic extremes reported codeine effects consistent with their genotype: the 2 PMs of codeine reported no analgesia as a result of taking codeine, whereas 2 of the 3 UMs reported immediate pain relief from codeine but stopped taking it due to dizziness and constipation. Much larger numbers are needed to study similar correlations among extensive and intermediate metabolizers.

Conclusions: In this pilot study, the extreme *CYP2D6* genotypes (PMs and UMs) seemed to predict pain response and adverse events. Larger sample sizes are needed to correlate the range of genotypes with pain response.

Key Words: CYP2D6, pharmacodynamics, codeine, analgesia, cesarean section, therapeutic drug monitoring

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INTRODUCTION

Pain is a major public health issue, and it is the most common reason for physician consultation in the United States.[1] In Canada, >30% of the population is afflicted with chronic pain, and approximately 5% are taking codeine to manage pain at any given time.[2] Despite a wide variety of pharmacological agents available on the market, many people cannot achieve optimal analgesia, and inadequate treatment remains a major cause of suffering and dissatisfaction in pain therapy.[3] One cause for the variable success of pharmacologic pain therapy is different genetic polymorphisms affecting patients' pharmacodynamic response to analgesics.

Codeine, a commonly used opiate, acts on the mu-opiate receptor predominantly via its metabolite morphine, which is formed almost exclusively by the genetically polymorphic enzyme cytochrome P450 2D6 (CYP2D6). Although, in most people, 10% of codeine is biotransformed into morphine, multiple copies and multiple variations of the *CYP2D6* gene affect the percentage of codeine conversion into morphine and hence the analgesia and toxic responses to codeine.[4] *CYP2D6* genetic variants can be associated with increased, normal, reduced or null enzyme function resulting in a wide range of phenotypic activity from excessive metabolism [ultrarapid metabolizers (UMs)] to normal metabolism [extensive metabolizers (EMs)] to partial metabolism [intermediate metabolizers (IMs)], to no metabolism of codeine [poor metabolizers (PMs)]. There are currently >80 major *CYP2D6* allelic variants described (http://www.cypalleles.ki.se/cyp2d6.htm). To simplify genotype interpretation, an activity score system that classifies individuals according to the number and functionality

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of their *CPY2D6* alleles can be used to predict their *CYP2D6* enzyme activity.[5,6]

Postpartum pain, due to either cesarean section (c-section) or episiotomy, is a major reason for the prescription of codeine, with an estimated 30% of North American women using the drug.[7] Several studies have examined the percent conversion of codeine into morphine for different CYP2D6 metabolizers, by measuring morphine serum concentrations as the endpoint.[3,6,8–12] These studies have identified that PMs convert very little codeine into morphine, whereas UMs can have plasma morphine concentrations about 50% higher than normal. However, there is much less information on the effect of *CYP2D6* polymorphism on codeine pharmacodynamics. Only 4 studies have examined the effect of *CYP2D6* on codeine analgesia: 2 using healthy volunteers[13,14] and 2 in a clinical setting.[15,16] Given the dearth of clinical studies, our objective was to study the relationship between *CYP2D6* genotype and codeine analgesia, specifically among women postpartum.

MATERIALS AND METHODS

Patients and Study Design

This was a nested cohort study within a recently published randomized controlled trial.[17] (Clinical Trial Register: ISRCTN79265996) in which 80 women who underwent elective c-section provided an ethylenediaminetetraacetic acid blood sample for *CYP2D6* genotype analysis. All pregnant women who were scheduled to have an elective c-section were approached during a routine prenatal visit at the obstetric clinic at St Michael's Hospital between September 1, 2008, and March 31, 2009. Research protocol and informed consent were approved by the Research Ethics Board at St Michael's Hospital.

All elective c-sections at St Michael's Hospital in Toronto were performed using the Pfannenstiel protocol.[18] Women who underwent elective c-sections received spinal anesthesia with 0.75% bupivicaine, and 15 mcg of fentanyl at induction, followed by 100 mcg of morphine administered epidurally at the end of surgery. Women were routinely monitored in hospital for 3 days and then discharged (ie, ~75 hours after surgery).

Post c-section, the following analgesia protocol was administered, unless noted otherwise:

1. *A nonsteroidal anti-inflammatory (NSAID):* naproxen (500 mg) rectally and then orally every 12 hours for 48 hours.
2. *For breakthrough pain:* acetaminophen (300 mg) with codeine (30 mg) and caffeine (15 mg) (Tylenol no. 3, Johnson & Johnson, New Brunswick, NJ), 1–2 tablets orally, every 4 hours pro re nata (prn).
3. *For mild to moderate pain*: acetaminophen (500 mg; Tylenol extra strength, Johnson & Johnson, New Brunswick, NJ), 1–2 tablets orally, every 4 hours prn.

All medication consumption was recorded. To evaluate the rate of postoperative recovery, we employed the Milestone Questionnaire, a scale used previously that comprises several items: time to first hunger, first spontaneous voiding, first ambulation, first bowel movement, and first eating solid foods after elective c-section.[19]

Outcome Measures

The primary endpoint for the study was the area under the curve (AUC) for pain in ambulation for days 1–3 using the visual analog scale (VAS),[20,21] corresponding to the patient's total pain. VAS scores were collected (4 times a day) ranging from 0 (no pain) to 10 (maximal pain) from all women while they were in the hospital. The area under the VAS–time curve (AUC of pain) was calculated by plotting the VAS scores over time and using the trapezoid rule.

The following 7 secondary outcome measures were collected or calculated: 3-day codeine dose (total and milligrams per kilogram of body weight), 3 day NSAID dose (total and milligrams per kilogram), number of adverse events, peak pain (AUC of VAS scores on day 2), codeine dose day 2, genotype-adjusted morphine dose, and mean VAS pain scores. The following 2 covariates were collected and used in the multivariate analysis: mother's age and neonate's birth weight.

Genotyping *CYP2D6*

Blood samples for DNA extraction were collected from mothers during a routine blood draw in triage on the labor ward and then stored at −80°C. The blood samples from those women who took codeine-containing medication were genotyped for the presence of 15 *CYP2D6* alleles [**2*, **3*, **4*, **5* (gene deletion), **6*, **7*, **8*, **9*, **10*, **12*, **14*, **17*, **29*, **41*, **XN* (gene duplication) by using AutoGenomics INFINITI Analyzer and the CYP450 2D6I Assay (AutoGenomics Inc, Vista, CA)]. These 15 polymorphisms are the most frequently occurring alleles identified; we included the most common alleles associated with poor (**3*, **4*, **5*, **6*), intermediate (**10*, **17*, **41*), and increased metabolism (gene duplications) in different ethnic populations.[22] Alleles not carrying any detected mutations were classified as **1* (wild type).

Assigning a CYP2D6 Activity Score

To predict the *CYP2D6* metabolizer phenotype, we used the activity score system[4,6] whereby alleles with full *CYP2D6* activity (**1*, **2*) are given a score of "1," alleles with reduced activity (**9*, **10*, **17*, **29*, **41*) a score of "0.5," and inactive alleles (**3*, **4*, **5*, **6*, **7*, **8*, **12*, **14*) a score of "0". A genotype activity score that was obtained by summing the scores of the individual alleles in a given genotype was used to classify patients in 4 *CYP2D6* phenotype classes as follows: PMs had an activity score of 0, IMs an activity score ranging from 0.5 to 1.5, EMs an activity score of 2, and patients carrying gene duplication in combination with 2 active alleles were classified as UMs.

Statistical Analyses

The statistical analyses were performed on SPSS software (IBM SPSS, version 17, Somers, NY). Descriptive statistics were calculated for the independent variables and were checked for normality. Multivariate and univariate (Spearman correlation) analyses were used to examine the relationship between *CYP2D6* genotype and analgesic response. Because our sample size was small and the codeine

dose was not normally distributed, we used Spearman correlation to examine the relationship between the dependent variable AUC of pain and the independent variable genotype-adjusted morphine dose. The multivariate analysis using linear regression with the stepwise method examined the correlation between the independent variable AUC of pain and the dependent variable genotype group (UM, EM, IM, or PM) derived from the genotype activity score, with the covariates of codeine dose (milligrams per kilogram), NSAID dose (milligrams per kilogram), mother's age, and neonate birth weight. For missing data, we used the last-observation-carried-forward method in the analysis of AUC and mean pain scores.

Model Estimation of Genotype-Adjusted Morphine Dose

To evaluate whether genotype-adjusted morphine dose per kilogram can predict analgesia levels in a univariate model, we used the *CYP2D6* activity score to estimate morphine dose.

Estimating Codeine Metabolism Rates

To estimate an individual's morphine dose, we commenced with the assumption that EMs (those with an activity score of 2) biotransform 10% of consumed codeine into morphine.[6] To account for genotype variability, a genotype-codeine conversion factor, as suggested by Kirchheiner et al,[6] was applied to the EM standard of 10% to account for increased or decreased morphine production according to the *CYP2D6* genotype. The factors were derived by taking the ratio of plasma AUC of morphine over plasma AUC of codeine for each *CYP2D6* (fine activity) genotype group[6]; ratios for the groups are as follows: UM (activity score of 3) = 0.095; EM (activity score of 2) = 0.064; IM (activity score of 1.5) = 0.032; and PM (activity score of 0) = 0.003. These ratios were indexed to the EM group to develop a genotype-codeine conversion factor: 1.5 for UM, 1 for EM, 0.50 for IM, and 0.05 for PM.

RESULTS

Of the 80 women in the original randomized controlled trial, a total of 45 took acetaminophen with codeine for pain relief. Two women were not prescribed naproxen as first-line medication for analgesia and were instead only prescribed acetaminophen with codeine. No women were taking *CYP2D6* or *CYP3A4* inhibiting medications during their hospital stay. The majority of women reported feeling pain most acutely during the second day after the c-section. Patient characteristics for the 45 women are shown (Table 1). Of these 45 women, 3 were UMs (7%), 2 were PMs (4%), 26 were IMs (58%), and 14 were EMs (31%) (Table 2).

During days 1 and 2, a total of 3 pain scores, which represented <1% of the data, were not collected because the patients were sleeping at the time of recording; all other data for patients were captured (pain medication consumption and time to first activity) on these days. However, on day 3, a total of 10 patients (22%) were discharged early (after 48 hours instead of after 75 hours in hospital) resulting in 22% missing data (pain scores, pain medication consumption, and time to first activity). The main endpoint (AUC of pain) and all other secondary measures were normally distributed, with the exception of codeine medication dose and adverse events, which were not normally distributed.

Three-day mean (±SD) pain AUC scores were 238 (±106) for the cohort; only the scores for the UMs seemed

TABLE 1. Patient Characteristics

Patient Characteristics	All Patients n = 45	UMs n = 3	EMs n = 14	IMs n = 26	PMs n = 2
Ethnicity					
White	17	0	7	8	2
Asian	14	0	2	12	0
Hispanic	8	1	3	4	0
African American	5	2	2	1	0
Arab	1	0	0	1	0
Maternal age (yrs)					
Median	34	22.6	34.5	34	35.5
Range	19–42	19–28	22–39	24–42	35–36
No previous c-sections					
Median	1	1	1	1	1.5
Range	0–3	1–1	0–2	0–3	1–2
Weight of neonates (g)					
Mean (±SD)	3463 (±77)	3580 (±557)	3548 (±483)	3438 (±550)	3027 (±38)
Range	2625–5315	3056–4165	2925–4400	2625–5315	3000–3054
Duration of c-section surgery (min)					
Mean (±SD)	41 (±1)	41 (±6)	41 (±12)	41 (±11)	37 (±6)
Gestational age of baby (wks)					
Mean (±SD)	38.3 (±0.1)	38.5 (±0.3)	38.6 (±0.1)	38.2 (±0.1)	37.8 (±0.4)
Median	38.5	38.5	38.5	38	37.8
Range	37–40.5	38–39	38–39	37–42.5	37.5–38

TABLE 2. CYP2D6 Allele and Genotype Frequencies, Activity Scores, and Predicted Phenotypes

Allele	Frequency	Allele	Frequency	Allele	Frequency
*1	30 (33%)	*6	0 (0%)	*12	0 (0%)
*2	18 (20%)	*7	0 (0%)	*14	0 (0%)
*3	0 (0%)	*8	0 (0%)	*17	3 (3%)
*4	14 (16%)	*9	1 (1%)	*29	1 (1%)
*5	2 (1%)	*10	15 (17%)	*41	6 (7%)

CYP2D6 Genotype	Frequency	Activity Score	Predicted Phenotype
*1/*2, *XN	1	>2	UM
*2/*2, *XN	1	>2	UM
*2/*17, *XN	1	≥2	UM
*1/*2	7	2	EM
*1/*1	5	2	EM
*2/*2	2	2	EM
*1/*10	4	1.5	IM
*1/*41	3	1.5	IM
*2/*10	2	1.5	IM
*2/*17	1	1.5	IM
*1/*4	6	1	IM
*10/*10	3	1	IM
*17/*29	1	1	IM
*2/*4	1	1	IM
*4/*41	2	0.5	IM
*4/*10	1	0.5	IM
*4/*9	1	0.5	IM
*5/*41	1	0.5	IM
*4/*4	1	0	PM
*4/*5	1	0	PM
Total	45		

higher 408 (±102). Three-day mean (±SD) pain scores for the cohort were 3.5 (±1.6); 3 genotype groups reported similar scores, with the exception of UM who reported 6.0 (±1.5). Three-day median codeine dose was 180 mg; this was the same for all genotype groups except for the PMs, which was 450 mg. Three-day genotype-adjusted morphine dose ranged from 0.007 to 1.1 mg/kg (Table 3).

Relation of Genotype to Pain Outcomes

Due to the very small number of extreme genotypes, this pilot study was underpowered to show the overall relationship between genotype and pain response. Multivariate analysis approached significance ($F = 7.615$, $r^2 = 0.15$) for the covariate of mother's age (beta = −7.736, $P = 0.06$) in explaining the AUC of pain. All other variables were nonsignificant: total codeine dose per kilogram ($P = 0.99$), total NSAID dose per kilogram ($P = 0.92$), neonate birth weight ($P = 0.98$), EM genotype group ($P = 0.99$), IM genotype group ($P = 0.96$), and PM genotype group ($P = 0.99$).

Similar results were achieved for multiple linear regression for peak pain (day 2), which was significant ($F = 4.600$, $r^2 = 0.097$) for mother's age (beta = −2.377, $P = 0.038$), whereas all other variables were nonsignificant: EM genotype group ($P = 0.99$), IM genotype group ($P = 0.96$), PM genotype group ($P = 0.99$), neonate birth weight ($P = 0.94$), day 2 NSAID dose milligrams per kilogram ($P = 0.95$), and day 2 codeine dose milligrams per kilogram ($P = 0.88$).

Analyses of Extreme Genotypes

Because the vast majority of patients were, as expected, EM and IM, we examined the pain and analgesia effects of our extreme cases (UMs and PMs). Pictorial representation of individual pain scores and codeine-containing medication consumption are shown (Fig. 1).

Ultrarapid Metabolizers

Each of the 3 UMs had 1 of the factors associated with increased perceived pain after c-section identified by us recently[17]; 2 were young (19 and 21 years old), and the third gave birth to a baby >4000 g. Despite the higher level of pain for these 3 women, 2 of the women requested only small doses of codeine-containing medication (60 mg once and 60 mg thrice, respectively) preferring, instead, to take acetaminophen and naproxen or naproxen alone for pain relief, due to dizziness and constipation. The third UM was not prescribed naproxen for 48 hours postsurgery as per protocol but instead was only prescribed codeine-containing medication prn to relieve pain. She took 540 mg of codeine-containing medication (60 mg, 9 times) throughout her 3-day hospital stay and, although she did not note any adverse effects, she had not yet had a bowel movement at the time that she was discharged from the hospital (75 hours postsurgery) (Table 3).

Poor Metabolizers

The 2 PMs were both >35 years old, a factor associated with less pain response after c-section. Despite lower pain levels, neither of these women reported any reduction in pain after consuming codeine-containing medication. One took 120 mg of codeine-containing medication (60 mg, twice) and then switched to acetaminophen because she did not feel that the codeine was relieving her pain. The other took 780 mg (60 mg, 13 times) over a 3-day period; although she also did not report any pain relief from codeine-containing medication, she had not yet had a bowel movement at the time of hospital discharge (75 hours postsurgery).

DISCUSSION

This study compared clinical pain relief among women of varying *CYP2D6* genotypes who took codeine-containing medication after an elective c-section.

In our randomized trial published recently,[17] we identified 2 factors associated with women's perception of pain after c-section: mother's age (negative correlation) and neonatal birth weight (positive correlation). When the AUC of pain was regressed against total codeine consumption, total NSAID consumption, *CYP2D6* genotype group, mother's age, and neonatal birth weight, the only significant factor was the mother's age. Older patients' experience of pain may differ from that of younger patients due to both physiological and psychological reasons, as has been suggested before.[23,24] In addition, older patients have been reported to enjoy more pain relief than younger patients have, although receiving the same dose of medication.[25]

TABLE 3. Pain Scores, Medication Dosing, Adverse Events, and Milestone Questionnaire Results

Results	All Patients n = 45	UMs n = 3	EMs n = 14	IMs n = 26	PMs n = 2
Three-d postoperative pain scores					
AUC mean (±SD)	238 (±106)	408 (±102)	226 (±102)	226 (±100)	232 (±41)
Mean (±SD)	3.5 (±1.6)	6.0 (±1.5)	3.3 (±1.5)	3.4 (±1.5)	3.4 (±1.0)
Median	3.4	6.5	3.1	3.4	3.3
Range	1.1–7.2	4.3–7.2	1.2–6.3	1.1–6.9	3.8–4.0
Count of women ≥4 mean VAS score	16	3	4	8	1
Day 2 (peak) postoperative pain scores					
AUC mean (±SD)	92 (±41)	159 (±31)	85 (±39)	89 (±39)	84 (±27)
Mean (±SD)	3.6 (±1.7)	6.5 (±1.5)	3.3 (±1.5)	3.5 (±1.6)	2.9 (±0.9)
Median	3.7	7.1	3.1	3.7	2.9
Range	0.8–7.7	4.9–7.7	1.1–6.4	0.8–7.0	2.3–3.6
Count of women ≥4 mean VAS score	18	3	5	10	0
3-d Codeine dose (mg)					
Median	180	180	180	180	450
Range	30–840	60–540	60–840	30–660	120–780
3-d Codeine dose (mg/kg)					
Median	2.4	3	2.2	2.4	4.6
Range	0.4–11.1	0.7–6.8	0.8–10.8	0.4–11.1	1.6–7.7
Day 2 codeine dose (mg/kg)					
Median	0.8	0.7	0.9	1	1.5
Range	0–4.6	0–3.8	0–4.6	0–3.7	0–3.0
Estimate 3-d morphine dose (mg/kg)					
Median	0.22	0.4	0.2	0.1	0.02
Range	0.007–1.1	0.1–0.9	0.08–1.1	0.02–0.8	0.007–0.04
Estimate day 2 morphine dose (mg/kg)					
Median	0.09	0.1	0.09	0.04	0.007
Range	0–0.5	0–0.5	0–0.5	0–0.2	0–0.001
No adverse events from codeine					
Median	0	1	0	0	0.5
Range	0–3	0–1	0–3	0–3	0–1

Time to First (hours, minutes)	Eating Solid Foods Mean (±SD)	Flatus Mean (±SD)	Bowel Movement Mean (±SD)	Ambulation Mean (±SD)	Spontaneous Voiding Mean (±SD)	Total Tylenol No 3 Dose mg (1 Dose = 60 mg)	When Tylenol No 3 Was Consumed
Group of 80		24 (±10:45)	20 (±12:30)	58 (±16)	17 (±5:15)	17:30 (±5:15)	
Cohort of 45 (those taking codeine medication)	25 (±12:30)	22 (±13)	60 (±13)	17:30 (±5)	17:30 (±5:15)		
UM #1 (**2/*17*, *XN)	14:05	13:05	75:00+	25:35	21:15	540	Throughout 3 d
UM #2 (**1/*2*, *XN)	18:55	12:25	57:25	23:25	23:25	60	Dose on first day
UM #3 (**2/*2*, *XN)	23:45	3:45	75:00+	20:45	20:45	180	Throughout 3 d
PM #4 (**4/*4*)	28:45	20:45	48:45	10:45	15:45	120	Both doses on first day
PM #5 (**4/*5*)	15:43	13:13	75:00+	13:13	13:13	780	Throughout 3 d

75:00+ denotes that this had not yet occurred at the time of hospital discharge; time reported in hours and minutes; minutes have been rounded to the nearest 5-minute intervals.

Our univariate and multivariate models examining *CYP2D6* genotype and codeine dose showed no correlation with AUC of pain. We used pain AUC scores as a measure of total pain as this metric is simple to calculate, easy to explain, and captures 2 dimensions of the pain (magnitude and duration) in a single continuous measurement.[26]

The lack of overall correlation between AUC of pain and genotype-adjusted morphine dose in the univariate and AUC of pain and codeine dose in the multivariate models is expected, due to the fact that most patients were EMs and IMs, with very small numbers of extreme cases in which *CYP2D6* genotype has shown large effects.

The potential effects of *CYP2D6* genotype was illustrated in the individual cases of UMs and PMs, providing valuable insight into patients in whom *CYP2D6* polymorphism is clinically relevant. Although 1 PM and 2 UMs had low doses of codeine-containing medication (ie, 120, 60, and 180 mg, respectively, over 3 days) to control breakthrough pain, the

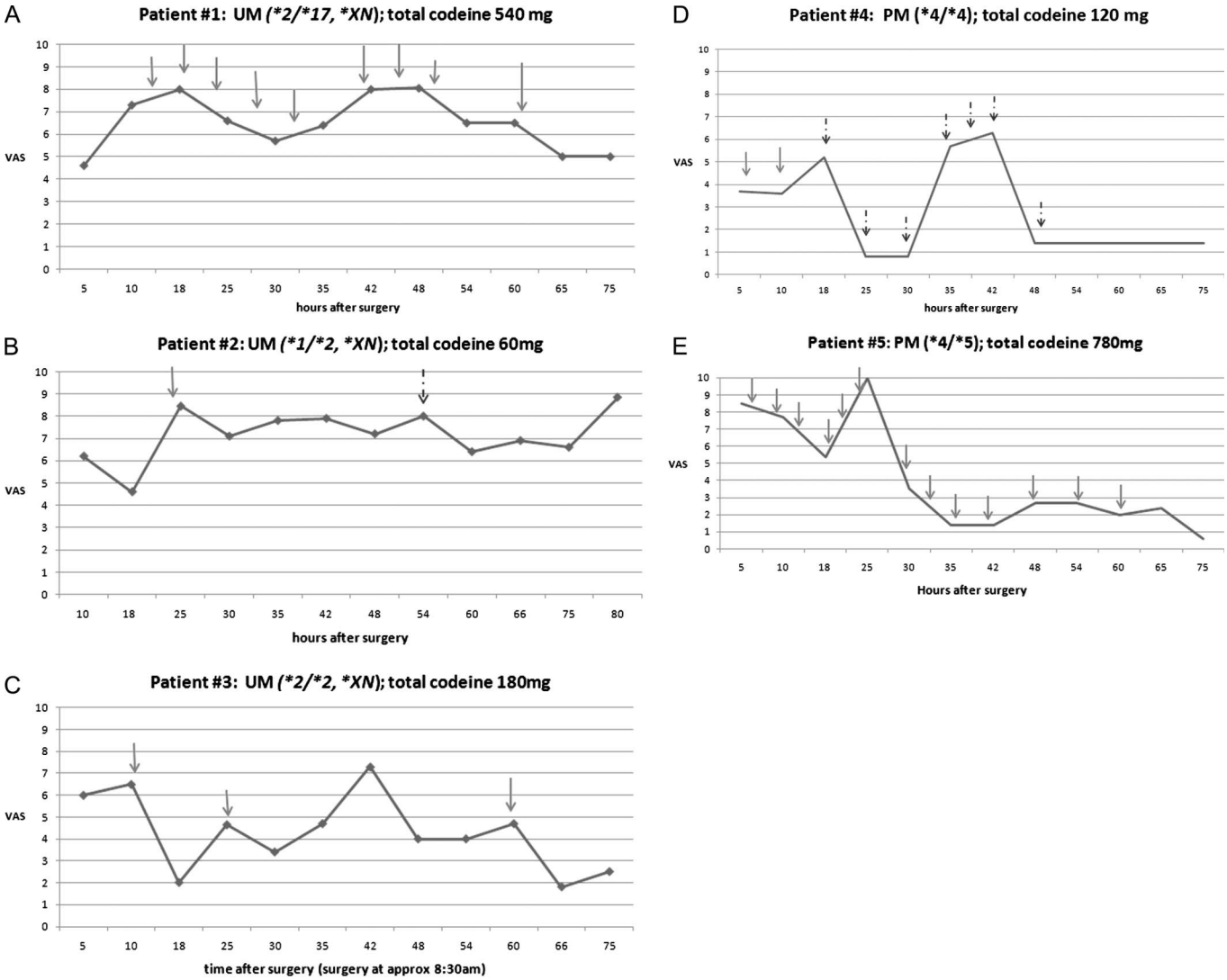

FIGURE 1. Individual pain scores and analgesia medication timeline for UMs and PMs of codeine. Solid arrows represent ingestion of Tylenol no 3 (60 mg), and broken arrows represent ingestion of Tylenol extra strength (1000 mg). In addition to the medication shown in the graphs, all the patients received NSAIDS for 48 hours postsurgery, except patient no 5.

reasons for these low doses were markedly different. Both UMs stopped taking the drug because of adverse effects, unlike the PM who stopped because she did not feel that the codeine-containing medication was helping her pain. In contrast, although the other PM also noted that the medication was not providing analgesia, instead, she repeatedly requested codeine-containing medication, until she was receiving the maximum daily dose (60 mg every 4 hours for 3 days). The one UM prescribed high doses of codeine-containing medication was, unfortunately, not prescribed naproxen as per the standard analgesia protocol, and as such was left with little option for pain relief. The 2 UMs and 1 PM that took codeine-containing medication throughout their 3-day hospital stay had not yet had a bowel movement at the time of hospital discharge; this length of time is outside the mean (±SD) time for the cohort (60 ± 13 hours). This is consistent with the finding in the previous literature showing that adverse effects arise from codeine ingestion, not just morphine, and occur regardless of *CYP2D6* genotype status.[13]

The strengths of this study include being one of the first studies to examine *CYP2D6* genotype and codeine analgesia in a clinical setting, and the first to do so postpartum. Since one researcher collected almost all of the pain score and secondary data, she was able to collect qualitative information about the patient's pain and why patients switched from one medication to another. By capturing patients' personal reactions, we were able to discern the differences between UMs and PMs who discontinued their codeine medication–capturing an important clinical distinction.

Potential limitations of this study include a very small underpowered sample, not measuring individual codeine metabolism rates, the inability to control for various other factors both genetic and nongenetic and the use of an NSAID in addition to codeine medication for analgesia. Firstly,

because the sample size was small, we did not have sufficient number of patients at the genetic extremes to identify a possible correlation to codeine analgesia.

Secondly, while we were able to secure a blood sample for genotyping during a routine blood draw prior to surgery, the vast majority of women were unwilling to provide additional blood samples for pharmacokinetics of codeine-containing medications for postpartum pain. A large interindividual variability in response to codeine has been reported in an experimental study among both extensive metabolizers[27] and intermediate metabolizers[28] and this has not been captured in this paper. In addition, the **1* allelic variant was assigned as a default if none of the other 14 alleles were present, so some rarer alleles could have been missed. Both of these conditions mean that the interpretation of genotypes and the resulting estimate of codeine and metabolites may be over or underestimated.

Thirdly, there are genetic factors which may modify the effect of morphine, including variability in the expression or signaling of the mu-opioid receptor,[29,30] variability in the MDR1 gene which codes for P-glycoprotein used for drug transport,[31] variability in other codeine metabolizing enzymes such as *CYP3A*,[32] and *UGT2B7*.[33]

Fourthly, there are also nongenetic effects such as variations in *CYP3A* activity due to pregnancy[34] and surgery[35] and nongenetic factors such as age, race, mood, and coping ability.[36] Moreover, large variability in the process of nociception[37] would lead to great interpatient variability in recorded pain scores and the desire for pain medication. The inability of the pain scores to differentiate patients may be due, in part, to issues other than pain severity. Concerns about adverse effects, medication interactions, and addiction, may all contribute to the decision to accept or reject treatment.[38]

Finally, while our analgesic protocol follows the WHO analgesic ladder for progressive treatment of increasing pain[39] this cannot lead to the assumption that the effect of the NSAID was similar across all women.

CONCLUSIONS

In this pilot study, extreme *CYP2D6* genotypes seemed to predict pain response or adverse effects. To study the impact of the whole range of genotype–phenotype combinations on the pharmacodynamics of codeine, these observations need to be confirmed in a much larger cohort, with higher proportions of UMs and PMs.

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