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Randomized Clinical Trial of Local Anesthetic Versus a Combination of Local Anesthetic With Self-Hypnosis in the Management of Pediatric Procedure-Related Pain

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A prospective controlled trial was conducted to compare the efficacy of an analgesic cream (eutectic mixture of local anesthetics, or EMLA) with a combination of EMLA with hypnosis in the relief of lumbar puncture-induced pain and anxiety in 45 pediatric cancer patients (age 6–16 years). The study also explored whether young patients can be taught and can use hypnosis independently as well as whether the therapeutic benefit depends on hypnotizability. Patients were randomized to 1 of 3 groups: local anesthetic, local anesthetic plus hypnosis, and local anesthetic plus attention. Results confirmed that patients in the local anesthetic plus hypnosis group reported less anticipatory anxiety and less procedure-related pain and anxiety and that they were rated as demonstrating less behavioral distress during the procedure. The level of hypnotizability was significantly associated with the magnitude of treatment benefit, and this benefit was maintained when patients used hypnosis independently.

Keywords: hypnosis, EMLA, pain, lumbar puncture, pediatric cancer

Pediatric cancers, in most cases, are not painful on their own. Young patients, however, as part of modern anticancer treatment and in the context of aggressive, long-term protocols, have to undergo numerous painful and invasive procedures for diagnosis, therapy, and supportive care. Children sometimes have one or more venipunctures daily; lumbar punctures (LPs) and bone marrow aspirations are often performed monthly. Young patients consider painful procedures to be the most difficult part of having cancer. Frequent repetition of procedures does not desensitize them to the distress, and if anything, some children show increased distress over time (Kellerman, Zeltzer, Ellenberg, & Dash, 1983).

In an LP, a fine-gauge needle is inserted between two lumbar vertebrae (generally the fourth and fifth) to enter the subarachnoid space. Cerebrospinal fluid is withdrawn for examination, and sometimes cytotoxic drugs are injected for therapeutic purposes. Patients must be in a curled-up position with the knees touching the chest, either seated or lying on one side so that the back is exposed. A nurse usually restrains the child to ensure that he or she remains correctly positioned and still. Extreme anxiety often occurs when the child feels the doctor's fingers probing for the proper site, the cold antiseptic agent, and finally the stinging, burning sensation as the needle is inserted. Conditioned anxiety is often observed in children prior to undergoing LPs, manifesting in a variety of ways such as irritability, depression, withdrawal, anorexia, insomnia, and avoidance of the clinic and staff. Afterwards, children can be withdrawn, angry, or embarrassed by their disruptive behavior (Katz, Kellerman, & Siegel, 1980). Research has indicated that the combination of a cancer diagnosis with associated invasive procedures and treatment protocols renders patients and their caretakers at risk for long-term psychological distress (often in the form of posttraumatic stress disorder), and this sometimes results in compromised treatment compliance (Kazak et al., 1997).

In terms of clinical management of painful procedures such as LPs and bone marrow aspirations, a recent survey of institutions belonging to the Pediatric Oncology Group (Broome, Richtmeier, Maikler, & Alexander, 1996) found that 67% of institutions routinely used only local anesthesia, 22% used systemic premedication, and 11% used different relaxation techniques. In 1998, the World Health Organization (WHO) developed and published guidelines for the management of pain in children with cancer. For all medical procedures, the use of a combination of a psychological with a pharmacological approach is supported. However, whether local anesthesia is best used in combination with psychological interventions such as hypnosis (which is the current WHO recommendation for the management of LPs) has never been tested empirically and warrants further investigation. Such an investigation is critical to include an attention control group; otherwise, the effect of the combined intervention can be attributed to nonspecific factors such as extra attention and demand characteristics.

Hypnosis has achieved status as an empirically validated, possibly efficacious intervention in the management of pediatric procedure-related cancer pain (Liossi, 2002) according to the Chambless and Hollon (1998) criteria. All studies conducted to

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date (Hawkins, Liossi, Ewart, Hatira, & Kosmidis, 1998; Hilgard & LeBaron, 1982; Katz, Kellerman, & Ellenberg, 1987; Kellerman et al., 1983; Kuttner, Bowman, & Teasdale, 1988; Liossi & Hatira, 1999, 2003; Wall & Womack, 1989; Zeltzer & LeBaron, 1982) found hypnosis effective in reducing the pain and anxiety of young patients during procedures. One study (Liossi & Hatira, 2003) attempted to teach young patients self-hypnosis. Although children were initially successful in reducing pain and anxiety, the effect was not maintained at the 6-month follow-up. Children indicated that they could have obtained better concentration had medical and nursing personnel conversed with them less. The investigators further speculated that the presence of parents in the treatment room might have unwittingly sabotaged children's efforts. In the absence of the therapist, parents may have responded verbally or nonverbally when they were seeing their child being treated and conveyed their own fears and apprehensions to the young patient. Such an interpretation is supported by the findings of Blount et al. (1989), who in their investigation of the relationship between adults' behavior and child coping concluded that adults' behaviors such as reassurance, apologizing, criticizing, and giving control typically preceded child distress. Currently, parental training programs, although successful in minimizing children's distress during procedures, are extensive and therefore costly (Blount, Powers, Cotter, Swan, & Free, 1994). If parents are capable of successfully implementing hypnotic interventions on their own or at least facilitating their child's efforts, the expense associated with having a clinician in the room to conduct the intervention could be minimized after parents are trained.

If hypnosis is the active agent in hypnotic treatment, then there should be a high correlation between hypnotizability and therapeutic outcome. Four studies examined the relationship between the child's hypnotizability and pain relief during painful medical procedures. Hilgard and LeBaron (1982) and Liossi and Hatira (1999, 2003) reported a significant positive relationship between hypnotizability and clinical benefit following hypnosis treatment. Wall and Womack (1989) found no such relationship. Hence, it remains unclear whether hypnosis is the active agent in these types of clinical interventions and also whether hypnotizability is still predictive of therapeutic outcome when hypnosis is used in combination with pharmacological interventions.

In terms of pharmacological management of painful procedures, a local anesthetic used for pediatric cancer patients is a eutectic mixture of local anesthetics, or EMLA cream. EMLA is a mixture of lidocaine and prilocaine, and when applied 45–60 min before the procedure, it causes complete dermal anesthesia and allows for effective tissue penetration. A number of investigators have evaluated EMLA (Halperin et al., 1989; Juarez-Gimenez et al., 1996; Kapelushnik, Koren, Solh, Greenberg, & DeVeber, 1990) with children undergoing LPs and have found it effective in significantly reducing subjective pain and distress ratings reported by parents and nurses.

Because EMLA and combinations of EMLA with psychological interventions such as hypnosis have not yet been compared with one another in a controlled manner (Liossi, 1999), the aim of the present study was to compare the efficacy of EMLA with a combination of EMLA with hypnosis in the relief of LP-induced pain and anxiety in pediatric cancer patients. The study also explored whether young patients can be taught and can use hypnosis independently as well as whether the therapeutic benefit depends on hypnotizability. More specifically, in the current study the following hypotheses were tested:

Hypothesis 1: The combination of hypnosis with local anesthesia will reduce pain, anxiety, and distress during LPs and anticipatory anxiety before the procedure more than local anesthesia alone.

Hypothesis 2: Self-directed use of hypnosis will reduce pain, anxiety, and distress during LPs and anticipatory anxiety before the procedure more than local anesthesia alone; the effect will be maintained at the 6-month follow-up.

Hypothesis 3: High hypnotizable children will reduce pain, anxiety, and distress during LPs and anticipatory anxiety before the procedure more than low hypnotizable children.

Method

Participants

The study received approval from the Ethics Committee of the Children's Hospital Aglaia Kyriakou and was conducted in the Hematology/Oncology Department of the Children's Hospital Aglaia Kyriakou, Athens, Greece. Eligible participants included Greek-speaking patients with leukemia or non-Hodgkin's lymphoma between the ages of 6 and 16 years who were undergoing regular LPs. Exclusion criteria for this study were (a) previous hypnosis treatment, (b) concurrent treatment during the project with analgesic or psychotropic medication, and (c) a major affective disorder or other psychiatric diagnosis. For three equally balanced experimental groups, a priori power calculations indicated that for a sample size of 45 the power of the test for a one-way analysis of variance with a large effect size (Cohen's $f = 0.60$) would have a power of .945 when testing against the standard .05 significance level. Medical staff referred 50 consecutive families to the research unit, informing the families that the research "would teach children, if randomized to the experimental group, hypnotic skills for coping with the pain and anxiety of repeated medical procedures." Of these 50 families referred, 5 declined. Two adolescent boys declined on the grounds that they could cope with the pain on their own, and two parents cited being too distressed with the cancer diagnosis to participate in a research study. One patient was excluded from the original sample because she did not meet the inclusion and exclusion criteria. Hence, the final sample size for the study was 45. Flow of patients through the trial is presented in Figure 1.

Design

Forty-five children with leukemia or non-Hodgkin's lymphoma (23 boys and 22 girls) who were undergoing LPs (LPs were chosen because the majority of children in an oncology hospital undergo them) were randomly allocated (1:1:1) with the use of a table of random numbers to one of three treatment groups: (a) The EMLA group (EMLA) was treated with EMLA cream applied to intact skin for approximately 60 min before the procedure; (b) the EMLA plus hypnosis group (EMLA + hypnosis) was administered EMLA cream and was also treated with hypnosis; (c) the EMLA plus attention group (EMLA + attention) was administered EMLA cream and met with the therapist for an equivalent time and session frequency as those in the EMLA + hypnosis group. The baseline measures of pain and both anticipatory and pain-related anxiety were taken after the patients had experienced five to six LPs. Thus, previous experience had provided opportunities for patients to become familiar with the procedure and to develop responses to pain and possibly to control such responses by individual coping methods.

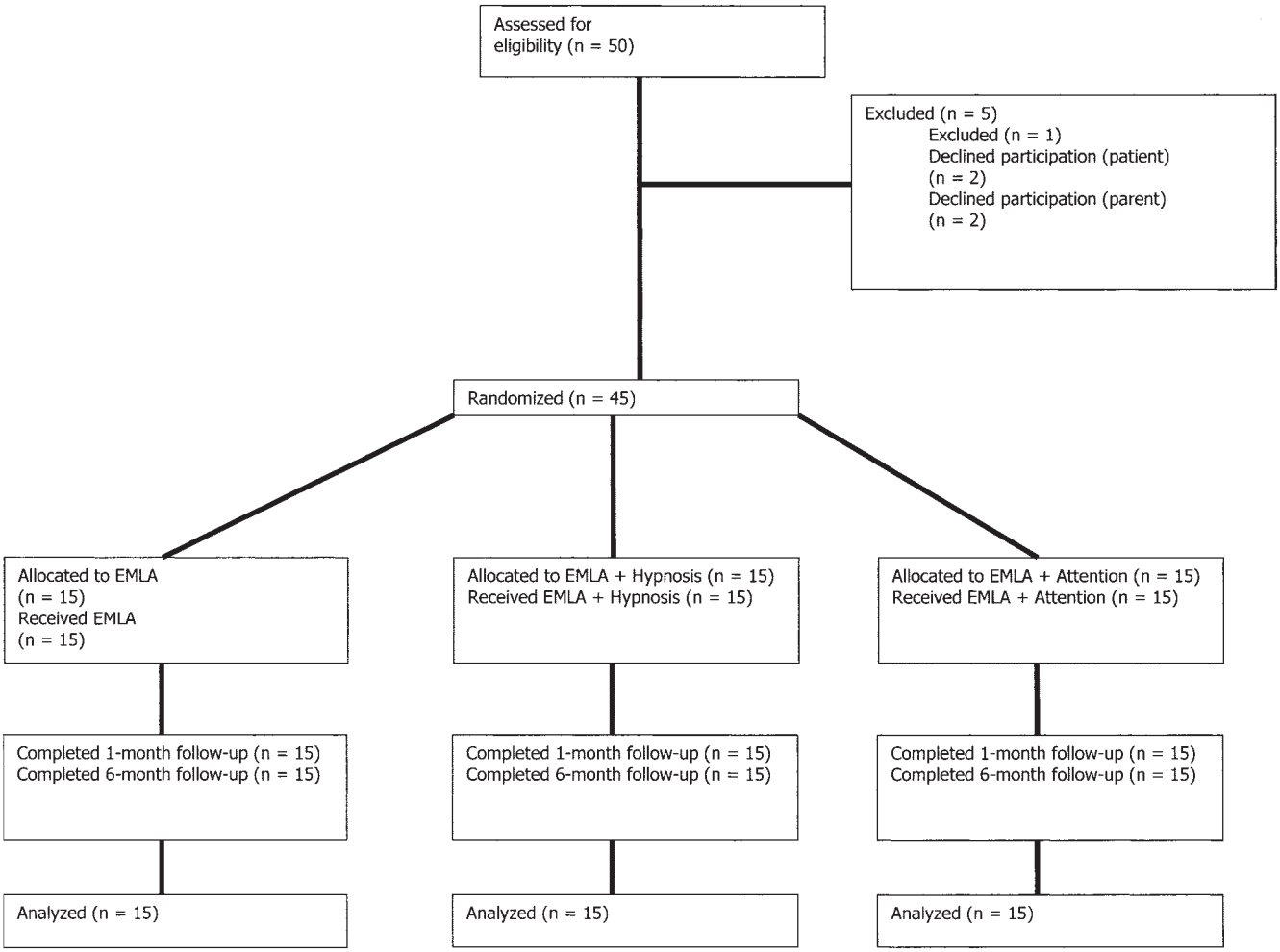

Figure 1. Flow of patients through the trial. EMLA = eutectic mixture of local anesthetics.

Measures

The Wong–Baker FACES Pain Rating Scale. The Wong–Baker FACES Pain Rating Scale (Wong & Baker, 1988) is a self-report measure and was used to assess anticipatory anxiety and procedure-related pain and anxiety. It is a 6-point faces rating scale in which Face 0 represents no pain (*no anxiety*) and Face 5 represents as much pain as the child can imagine (*as much anxiety as the child can imagine*). It has good reliability and validity, and discriminative validity for pain and fear–anxiety has been demonstrated.

The Procedure Behavior Checklist (PBCL; LeBaron & Zeltzer, 1984). This structured behavior observation instrument requires observers to document the presence and rate the intensity (on a 1–5 scale) of discomfort reactions to pain or anxiety (e.g., pain verbalized, screams, anxiety verbalized, physical resistance) during an invasive procedure. It is appropriate for use with children between 6 and 18 years and has good reliability and validity. Scores can range from 0 to 24.

The Stanford Hypnotic Clinical Scale for Children (SHCS–Children). A Greek translation of the SHCS–Children developed by Morgan and Hilgard (1978/1979) was administered to obtain a hypnotic susceptibility score. The SHCS–Children is a 20-min, 7-item scale that is administered to the participants individually. SHCS–Children scores are based on the assessment of both behavior and experience (via verbal reports) and range from 0 to 7. The Greek translation has good psychometric properties (Liossi & Hatira, 1995).

Procedure

The study involved six procedural steps: (a) assessment of the degree of anticipatory anxiety and procedure-related pain and anxiety during one LP at baseline; (b) measurement of hypnotizability; (c) interventions; (d) assessment of the degree of anticipatory anxiety and procedure-related pain and anxiety during the first LP in which interventions were used; (e) training session in which self-hypnosis was taught to patients in Group EMLA + hypnosis; and (f) assessment of the degree of anticipatory anxiety and procedure-related pain and anxiety during the first and sixth LPs in which self-hypnosis was used. These are discussed in turn and are presented graphically in Figure 2.

Assessment of the degree of anticipatory anxiety and procedure-related pain and anxiety during one LP at baseline (Time 1, or T1). During the baseline period (one LP)[1] within 10 min after the application of the local anesthetic, patients were asked by a research assistant for a self-rating of anxiety on the Wong–Baker FACES Pain Rating Scale. At the time of the LP, an independent observer (trained nurse) was present and completed the PBCL. After the entire procedure was over and patients had recovered (usually within 5 min), they were asked by the nurse for a retrospective

[1] Previous research (Liossi & Hatira, 2003) has demonstrated that there is minimal (nonsignificant) variation of experienced pain and anxiety among consecutive LPs after 5–6 procedures.

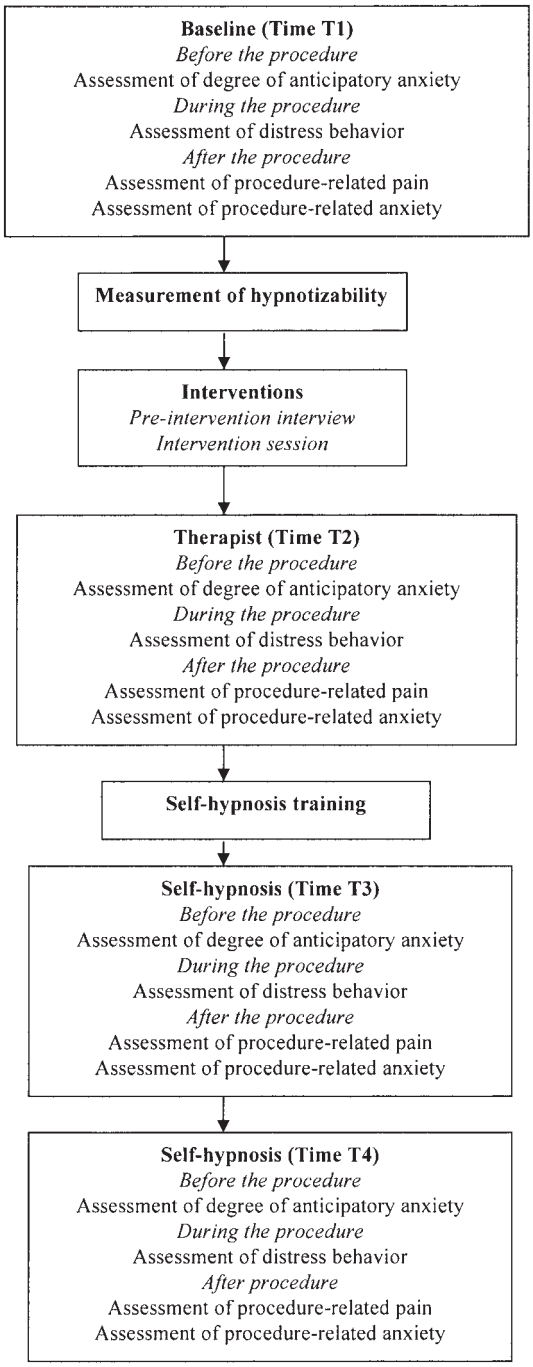

Figure 2. Schematic representation of the trial's procedure.

self-rating of pain and anxiety on the faces rating scale. Parents and health care professionals were asked to refrain from asking how the child felt after the procedure until the nurse had obtained the child's pain and anxiety rating of the LP.

Measurement of hypnotic ability. At a hypnotic assessment session, a Greek translation of the SHCS–Children was administered to obtain a hypnotic susceptibility score.

Interventions. In a preintervention interview, the therapist (Christina Liossi) obtained information about the child such as likes and dislikes, significant experiences, fears, hopes, and comfort areas; clarified the child's ideas and misconceptions, if any, about hypnosis; and established rapport. In the subsequent session (the second session overall, which we called the intervention session and which usually occurred within a week of the preintervention session), the patient was introduced either to hypnosis or to the attention control condition. Hypnosis and attention control protocols were comparable in terms of amount of therapist time spent with patients. The intervention session was approximately 40 min in duration for both EMLA + hypnosis and EMLA + attention groups. The therapist (Christina Liossi) remained blind to the preintervention data.

For the EMLA + hypnosis group the hypnotic induction procedure was adapted according to the child's age, interests, and cognitive and social development (Olness & Gardner, 1988). References to patient well-being, strengths, competence, and comfort were also included in the inductions. Following several minutes of hypnotic involvement, the patient was given "analgesic suggestions," including request for numbness, topical anesthesia, local anesthesia, glove anesthesia, and switchbox. The session ended with a posthypnotic suggestion that the hypnotic experience would be repeated and would provide comfort during the actual medical procedure, when the therapist would stroke the child's cheek. It was also mentioned that the application of EMLA 60 min before the LP would be an additional cue for the child to start relaxing and start feeling calm and ready for the procedure to follow.

For the EMLA + attention group, elements of the intervention included development of rapport, nonmedical play, and nonmedical verbal interactions. New coping skills were not introduced. During sessions, child and therapist were usually discussing school and extracurricular activities as well as playing board games or assembling model airplanes or building brick walls, depending on the child's age and interests. Overall, the therapist was supportive and warm, encouraged the child to express freely his or her interests, and formed a close relationship with the child.

All patients received standard interventions provided by the hospital staff for pain control during LPs (i.e., medical and nursing staff offered information, support, and reassurance, and EMLA cream was applied approximately 60 min before the procedure).

The first LP (Time 2, or T2) was scheduled within 5 days after completion of the intervention. In all cases, including controls, the child and his or her parent (if present) were accompanied to the treatment room by the therapist. The therapist positioned herself at the child's head, across from the doctor performing the procedure. A parent (generally the mother) was present for 95% of the study sample, with the parent situated at the head of the treatment table between the therapist and the doctor.

Assessment of anticipatory anxiety and procedure-related pain and anxiety during one LP with interventions (T2). Within the treatment room, for one LP (T2) all the same observations (by a different nurse from the one at baseline) and self-reports of anticipatory anxiety and procedure-related pain and anxiety were obtained as in the baseline observations. To keep the doctor performing the procedure and the behavioral observer blind as to the treatment condition, we used a nonverbal cue for all patients in the treatment room, with the therapist stroking each child's cheek. This served as a signal for children in the EMLA + hypnosis group to use their skills. Verbal communication from therapist to child during the procedure comprised brief encouragements (e.g., "You're doing fine," "It's almost over") and was the same for patients in all three groups. Parents and health care professionals, in all treatment conditions, were asked to refrain from attempting to comfort the child, in any way, and to let the therapist be in charge of the child's support during the procedure. The therapist (Christina Liossi) was present for all patients in all groups to minimize the effect of the presence of this individual. After completion of the procedure, but before formal assessment of pain and anxiety, the therapist excused herself and left the room so as to avoid influencing the patient's self-report.

Self-hypnosis training. In one 45-min session, children in the EMLA + hypnosis group were taught self-hypnosis following Gardner's (1981) model. Patients in the EMLA + attention group met with the therapist for an equivalent amount of time. This session was similar in

structure and content to the one conducted with children in the EMLA + attention group during the intervention phase.

Parents were requested during LPs at Times 3 and 4 (T3 and T4) to stroke the child's cheek (this allowed parents to actively comfort their child during the procedure and provided a cue for children in the hypnosis group to use their hypnotic skills) and to refrain from overreassurance and communicate brief encouragements (e.g., "You're doing fine," "It's almost over"). Similarly, medical and nursing professionals were requested to offer information, if necessary, and briefly encourage the child to remain still and calm.

Assessment of anticipatory anxiety and procedure-related pain and anxiety during LPs with self-hypnosis (T3, T4). All of the same types of observations and self-reports of anticipatory anxiety and procedure-related pain and anxiety were obtained, as in the baseline observations, for the first and sixth LPs in which self-hypnosis was used (T3 and T4, respectively). The therapist (Christina Liossi) was not present for any of those procedures.

Methodological Considerations

PBCL reliability. For 54 procedures (30%), randomly distributed throughout the course of the trial, a second behavioral observer (a psychology graduate student) was present in the treatment room and completed independently the PBCL.

Degree of blindness. It was expected that group membership would not be transparent to observers in the procedure room because children in the EMLA + hypnosis group were not actively coached by the experimenter or their parent during the LP (T2, T3, T4). Nevertheless, after observers had completed the measurements and were coming out of the treatment room, a research assistant asked them to guess the patient's group membership.

Treatment fidelity. In line with recommendations by Moncher and Prinz (1991) to ensure uniform and consistent application of the treatment across patients, a treatment manual was prepared that described in detail the interventions for each of the three experimental conditions and the procedural steps of the present investigation.[2] All of the interventions were provided by the same trained therapist (Christina Liossi). Adherence to the treatment protocol was ensured by direct observation and analysis of sessions. Twenty intervention procedures (including sessions with children in the office and the treatment room) were randomly selected and rated for adherence by a research assistant, who was not otherwise involved in the study. The assistant was present in the treatment sessions and rated the compliance of the therapist's intervention in comparison to the one described in the treatment manual on a 10-cm visual analogue scale ranging from 0 (*treatment completely different from the one prescribed in the treatment manual*) to 10 (*treatment exactly as prescribed in the treatment manual*).

Results

Reliability of PBCL

Interrater reliability checks for the behavioral observations (observed distress) were conducted for 30% of the procedures. Pearson's correlation coefficient was found to be .98 ($p < .001$), and there was no systematic difference between observers, $t(53) = 0.73$, $p = .47$, two-tailed.

Degree of Blindness

Thirty-five procedures (29.9%) randomly distributed throughout the trial were monitored for blindness. Observers could not distinguish reliably between children who were in the EMLA + attention, the EMLA, or the EMLA + hypnosis group, $\chi^2(4, N = 35) = 3.69$, $p = .45$, Cramer's $V = .23$). This can be attributed to the fact that hypnosis was not performed in the treatment room and also that children respond to hypnosis in a different way than adults do (e.g., sometimes they keep their eyes open, move, and make spontaneous comments during hypnosis).

Treatment Fidelity

The mean concordance between the therapist's treatment and the treatment protocol was judged to be 8.5, with a standard deviation of 0.6. Most commonly reported deviations of the actual treatment from the one described in the treatment manual included the therapist providing physical contact in response to a patient's request and brief discussions about the child's activities and interests such as school and sports. The reported compliance rate is considered satisfactory because in pediatric clinical research minor variations are both necessary and inevitable to maintain rapport with patients and provide ethical, compassionate care.

Self-Reported Anticipatory Anxiety, Procedure-Related Anxiety, and Pain and Observed Distress

The primary analysis was intention to treat and involved all patients who were randomly assigned to the three groups. Randomization resulted in homogeneous groups of patients; there were no significant differences among the three groups in key characteristics, including baseline anticipatory anxiety, $F(2, 42) = 0.06$, $p = .94$, $\eta_p^2 < .01$; procedure-related pain, $F(2, 42) = 0.37$, $p = .69$, $\eta_p^2 = .02$; procedure-related anxiety, $F(2, 42) = 0.06$, $p = .94$, $\eta_p^2 < .01$; distress levels, $F(2, 42) = 0.56$, $p = .58$, $\eta_p^2 = .03$; hypnotizability, $F(2, 42) = 0.68$, $p = .51$, $\eta_p^2 = .03$; and demographic characteristics, including sex, $\chi^2(2, N = 45) = 2.31$, $p = .31$, and age, $F(2, 42) = 0.08$, $p = .92$, $\eta_p^2 < .01$. The mean age (standard deviation) of the sample was 8.84 (2.86) years. The mean hypnotizability (standard deviation) score was 4.48 (2.65).

Table 1 summarizes the sample means and standard deviations at T1 to T4 for anticipatory anxiety, procedure-related pain, procedure-related anxiety, and observed distress by group.

The design under consideration is a doubly multivariate 3 × 4 mixed design with four noncommensurate dependent variables. The between-subjects factor is group, with three levels (EMLA, EMLA + hypnosis, EMLA + attention); the repeated measures factor is time, with four levels (T1 is baseline, T2 is therapist, T3 is self 1, T4 is self 2); and there are four dependent variables (anticipatory anxiety, procedure-related anxiety, procedure-related pain, observer's report). With reference to Wilks's lambda, there was a statistically significant, doubly multivariate interaction between time and group, Wilks's $\Lambda = 0.03$, multivariate $F(24, 62) = 11.49$, $p < .001$, $\eta_p^2 = .82$; a significant main effect due to group, Wilks's $\Lambda = 0.09$, multivariate $F(8, 78) = 22.06$, $p < .001$, $\eta_p^2 = .69$; and a significant main effect due to time, Wilks's $\Lambda = 0.05$, multivariate $F(12, 31) = 46.96$, $p < .001$, $\eta_p^2 = .95$.

Following the multivariate test of significance, the univariate effects of treatment on self-reported anticipatory anxiety, self-reported procedure-related anxiety, self-reported procedure-related pain, and observed distress were assessed via four 3 × 4 mixed analyses of variance (ANOVAs) with group as the between-patient factor with three levels (EMLA, EMLA + hypnosis, EMLA +

[2] The treatment manual is available upon request from Christina Liossi.

Table 1
Pain, Anxiety, and Distress Outcomes at Baseline (T1), Therapist (T2), and Self (T3, T4) Phases

	M				*SD*			
Group	T1	T2	T3	T4	T1	T2	T3	T4
Self-reported anticipatory anxiety								
EMLA + attention	4.73	3.53	3.40	3.33	0.59	0.52	0.51	0.62
EMLA + hypnosis	4.73	0.40	0.53	0.47	0.59	0.63	0.64	0.64
EMLA	4.67	3.53	3.60	3.20	0.62	0.52	0.74	0.86
Procedure-related self-reported pain								
EMLA + attention	4.60	2.67	2.33	2.13	0.74	1.05	0.98	0.99
EMLA + hypnosis	4.60	1.27	0.93	1.07	0.74	0.80	0.59	0.70
EMLA	4.40	2.73	2.27	2.20	0.74	0.46	0.59	0.56
Procedure-related self-reported anxiety								
EMLA + attention	4.73	2.13	2.27	2.13	0.59	0.74	0.80	0.74
EMLA + hypnosis	4.73	0.40	0.40	0.40	0.59	0.63	0.63	0.63
EMLA	4.67	3.20	2.60	2.47	0.62	0.86	0.99	0.99
Observed distress								
EMLA + attention	16.73	13.33	12.33	12.00	3.84	2.79	2.50	2.65
EMLA + hypnosis	15.33	7.40	7.00	6.60	4.78	3.22	3.23	3.09
EMLA	16.60	13.40	12.73	12.27	3.22	2.56	2.28	2.46

Note. The higher the score, the greater the experienced pain, anxiety, and distress. EMLA = eutectic mixture of local anesthetics; T1, T2, T3, and T4 = Times 1, 2, 3, and 4, respectively.

attention) and with time as the within-patient factor with four levels (baseline, therapist, Self 1, and Self 2). To partly control for chance effects, we used a Bonferroni corrected significance level of .0125 (.05/4) in assessing the significance of effects. In all four instances, Mauchly's test of sphericity was significant (which indicates that the assumptions behind ANOVA had been violated), and the Greenhouse–Geisser epsilon correction factor was used for the analyses.[3] For all the analyses, SPSS for Windows Version 12 was used (SPSS, 2004).

Self-reported anticipatory anxiety. Figure 3 presents the average self-reported anticipatory anxiety as a function of time and group. From a visual inspection of the data it appears that only patients in the EMLA + hypnosis condition received benefit during the therapist and self phases. The 3 × 4 ANOVA indicated statistically significant main effects for time, $F(2.26, 95.05) = 213.78$, $p < .001$, $\eta_p^2 = .84$; and group, $F(2, 42) = 127.26$, $p < .001$, $\eta_p^2 = .86$; and a significant interaction effect between group and time, $F(4.53, 95.05) = 42.03$, $p < .001$, $\eta_p^2 = .67$. Between-subjects t tests (two-tailed) were done to determine the pairs of treatment means that were significantly different from one another. At T2, there was no mean difference between the EMLA group and the EMLA + attention group, $t(28) = 0.00$, $p = 1.00$, $\eta_p^2 = .00$. There was a statistically significant difference between the EMLA + hypnosis and the EMLA groups, $t(28) = 14.86$, $p < .001$, $\eta_p^2 = .89$; and the EMLA + hypnosis and the EMLA + attention groups, $t(28) = 14.86$, $p < .001$, $\eta_p^2 = .89$. At T3, the mean levels of anticipatory anxiety in the EMLA + hypnosis group were significantly lower than those in the EMLA group, $t(28) = 12.17$, $p < .001$, $\eta_p^2 = .84$; and the EMLA + attention group, $t(28) = 13.60$, $p < .001$, $\eta_p^2 = .84$. There was no significant difference between the EMLA group and the EMLA + attention group, $t(28) = 0.87$, $p = .39$, $\eta_p^2 = .03$. These same conclusions were obtained at T4.[4]

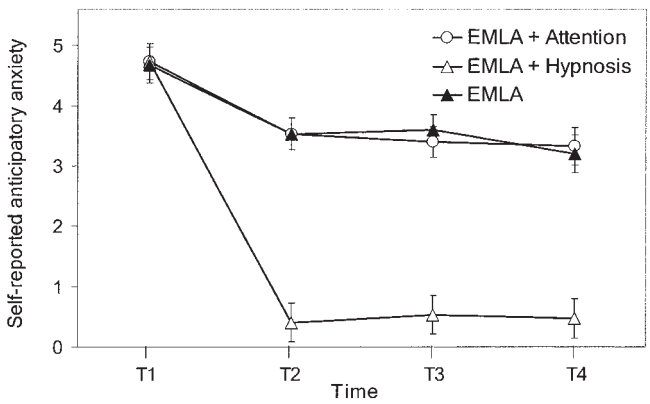

Figure 3. Mean self-reported anticipatory anxiety (95% confidence interval) across time for all groups. EMLA = eutectic mixture of local anesthetics; T1, T2, T3, and T4 = Times 1, 2, 3, and 4, respectively.

Procedure-related self-reported anxiety. Figure 4 presents the average procedure-related self-reported anxiety as a function of time and group. From a visual inspection of the data it appears that patients in the EMLA + hypnosis and the EMLA + attention conditions received benefit during the therapist and self phases. The 3 × 4 ANOVA indicated that there were significant main effects for time, $F(1.54, 64.55) = 361.14$, $p < .001$, $\eta_p^2 = .90$; and

[3] In fact, in the analyses that follow, application of the ultraconservative lower bound correction leads precisely to the same conclusions.

[4] Full results are available from Christina Liossi upon request.

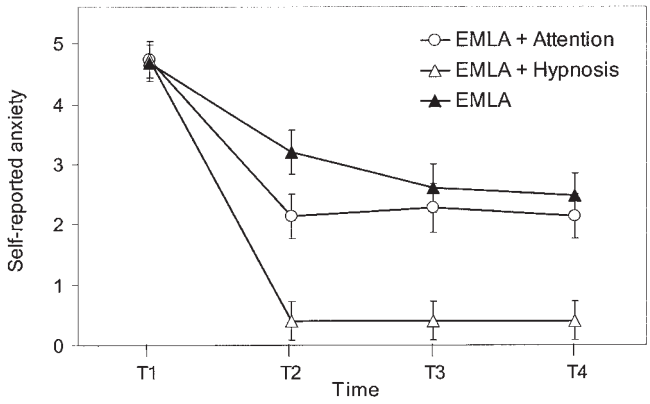

Figure 4. Mean procedure-related self-reported anxiety (95% confidence interval) across time for all groups. EMLA = eutectic mixture of local anesthetics; T1, T2, T3, and T4 = Times 1, 2, 3, and 4, respectively.

group, $F(2, 42) = 34.98$, $p < .001$, $\eta_p^2 = .63$; and a significant interaction effect between group and time, $F(3.07, 64.55) = 24.01$, $p < .001$, $\eta_p^2 = .53$. Between-subjects t tests (two-tailed) were performed to identify pairs of treatment means that were significantly different from one another. At T2, the mean self-reported anxiety in the EMLA + attention group was significantly lower than the mean in the EMLA group, $t(28) = 3.63$, $p = .001$, $\eta_p^2 = .32$. There was a significantly lower mean for the EMLA + hypnosis group compared with the EMLA group, $t(28) = 10.14$, $p < .001$, $\eta_p^2 = .79$; and for the EMLA + hypnosis group compared with the EMLA + attention group, $t(28) = 6.88$, $p < .001$, $\eta_p^2 = .63$. At T3, the mean level of anticipatory anxiety in the EMLA + hypnosis group was significantly lower than the EMLA group, $t(28) = 7.28$, $p < .001$, $\eta_p^2 = .65$; and significantly lower than the EMLA + attention group, $t(28) = 7.10$, $p < .001$, $\eta_p^2 = .64$. Also at T3, there was no significant difference in the mean self-reported anxiety levels between the EMLA group and the EMLA + attention group, $t(28) = 1.02$, $p = .32$, $\eta_p^2 = .04$. These same conclusions were drawn from the data at T4.

Procedure-related self-reported pain. Figure 5 presents the average procedure-related self-reported pain as a function of time and group. From a visual inspection of the data, it appears that patients in all groups received benefit during the therapist and self phases with the EMLA + Hypnosis group experiencing less pain. The 3 × 4 ANOVA indicated main effects for time, $F(1.84, 77.45) = 222.75$, $p < .001$, $\eta_p^2 = .84$; and group, $F(2, 42) = 13.78$, $p < .001$, $\eta_p^2 = .40$; and a significant interaction effect between group and time, $F(3.69, 77.45) = 7.63$, $p < .001$, $\eta_p^2 = .27$. Two-tailed between-subjects t tests were done to determine the pairs of treatment means that were significantly different from one another. In each instance, the mean level of procedure-related pain in the EMLA + hypnosis group was found to be lower than that in the EMLA + attention group: T2, $t(28) = 4.12$, $p < .001$, $\eta_p^2 = .38$; T3, $t(28) = 4.75$, $p < .001$, $\eta_p^2 = .45$; T4, $t(28) = 3.40$, $p = .002$, $\eta_p^2 = .29$; and lower than that in the EMLA group: T2, $t(28) = 6.17$, $p < .001$, $\eta_p^2 = .58$; T3, $t(28) = 6.15$, $p < .001$, $\eta_p^2 = .58$; T4, $t(28) = 4.88$, $p < .001$, $\eta_p^2 = .46$. There was no difference between the EMLA and EMLA + attention groups at any point in time: T2, $t(28) = 0.23$, $p = .82$, $\eta_p^2 < .01$; T3, $t(28) = 0.23$, $p = .82$, $\eta_p^2 < .01$; T4, $t(28) = 0.23$, $p = .82$, $\eta_p^2 < .01$.

Observer's report. Figure 6 presents the average observer's report as a function of time and group. From a visual inspection of the data, it appears that patients in all groups received benefit during the therapist and self phases, with the EMLA + hypnosis group expressing less behavioral distress. The 3 × 4 ANOVA showed that there were significant main effects for time, $F(1.25, 52.38) = 224.84$, $p < .001$, $\eta_p^2 = .84$; and group, $F(2, 42) = 12.23$, $p < .001$, $\eta_p^2 = .37$; and a significant interaction effect between group and time, $F(2.49, 52.38) = 15.80$, $p < .001$, $\eta_p^2 = .43$. Between-subjects t tests (two-tailed) were done to determine the pairs of treatment means that were significantly different from one another. At T2, there was a significantly lower mean level of distress in the EMLA + hypnosis group than in the EMLA group, $t(28) = 5.65$, $p < .001$, $\eta_p^2 = .53$; and a lower mean level of distress in the EMLA + hypnosis group compared with the EMLA + attention group, $t(28) = 5.38$, $p < .001$, $\eta_p^2 = .53$. The same conclusions were drawn from the data at T3 and T4. There was no statistically significant difference in the mean level of observed distress between the EMLA group and the EMLA + attention group over the four time periods.

Hypnotizability as related to therapeutic benefit. To determine the effect that hypnotizability had on the therapeutic outcome, we calculated correlations between hypnotizability scores and thera-

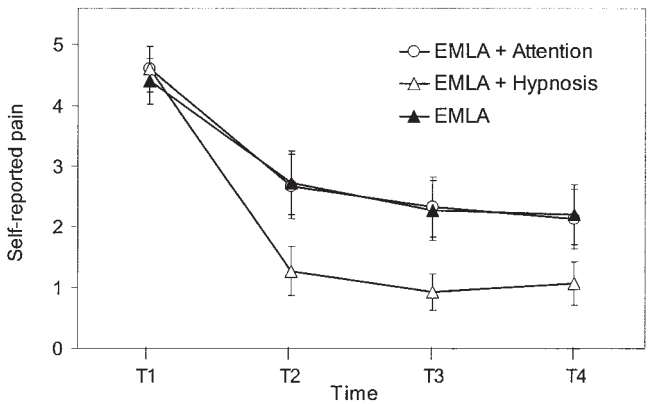

Figure 5. Mean self-reported procedure-related pain (95% confidence interval) across time for all groups. EMLA = eutectic mixture of local anesthetics; T1, T2, T3, and T4 = Times 1, 2, 3, and 4, respectively.

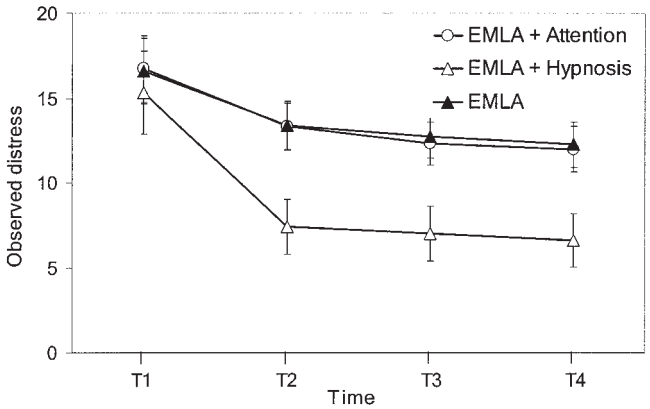

Figure 6. Mean observed distress (95% confidence interval) across time for all groups. EMLA = eutectic mixture of local anesthetics; T1, T2, T3, and T4 = Times 1, 2, 3, and 4, respectively.

peutic benefit, that is, reduction of the outcome measures between T1 and T2. For each patient, a difference score was obtained by subtracting T1 scores from T2 scores for each of the dependent variables, that is, procedure-related pain, procedure-related anxiety, anticipatory anxiety, and behavioral distress. Pearson correlation coefficients were calculated for SHCS–Children scores and for procedure-related pain reduction, procedure-related anxiety reduction, anticipatory anxiety reduction, and behavioral distress reduction. Correlations (two-tailed) were significant only for the EMLA + hypnosis group: pain, $r = .50$, $p = .05$; anxiety, $r = .66$, $p = .01$; anticipatory anxiety, $r = .66$, $p = .01$; observer's report, $r = .13$, $p = .63$.

Discussion

The present study investigated the efficacy of a combined pharmacological–psychological approach in the management of pediatric procedure-related cancer pain, and the results obtained provide strong experimental evidence for the current WHO (1998) clinical management guidelines. The combination of hypnosis with local anesthesia was found superior to local anesthesia in the reduction of anticipatory anxiety and procedure-related pain, anxiety, and distress behavior in children with cancer undergoing LPs. Further, the extent of benefit was superior to that of attention control patients. By not performing hypnosis in the treatment room and by monitoring the extent of blindness, we ensured that observers could not reliably distinguish patients in different groups. Moreover, self-reported data mirrored observational data. These methodological considerations reinforce the validity of the results and exclude the possibility of bias in the measurement of the outcome measures.

An important finding of this study that has been neglected in previous investigations is that when implementing a procedure-related pain-management program it is critical to consider anticipatory anxiety. Apparently, the application of a local anesthetic can become a conditioned stimulus, and children can be distressed for up to an hour before the procedure. The introduction of a psychological intervention helps children to remain calm during the time period between the application of the local anesthetic and the actual procedure.

As hypothesized and in line with previous studies (Hawkins et al., 1998; Hilgard & LeBaron, 1982; Katz et al., 1987; Kellerman et al., 1983; Kuttner et al., 1988; Liossi & Hatira, 1999, 2003; Wall & Womack, 1989; Zeltzer & LeBaron, 1982), hypnosis was found effective in reducing pain, anxiety, and distress during the actual procedure. From the results of this investigation, it is clear that contact with a therapist yields little benefit by itself. The only time that attention was sufficient to modify an outcome measure was when the presence of the therapist in the treatment room was effective in reducing procedure-related anxiety. This effect can be attributed to the fact that the therapist was supportive and refrained from reassurance, criticism, and other behaviors documented to increase children's distress during procedures (Blount et al., 1994), while parents and health care professionals remained in the background.

One of the questions that the present investigation aimed to answer is whether self-hypnosis might be a time- and cost-effective method that nevertheless extends the benefits of traditional heterohypnosis. In this regard, the findings, unlike the ones of a previous study (Liossi & Hatira, 2003), are encouraging. Across self-report and observed indices of distress, benefit was maintained at the 6-month follow-up when patients used self-hypnosis. An important finding is that parents, when minimally trained along with their children, can successfully facilitate self-regulatory pain-management interventions during medical procedures. The distress reductions obtained in the present study compare favorably to the results obtained by Blount et al. (1994) with much more extensive parent-training programs. Moreover, it could be that by participating in activities that serve to reduce their child's distress, parents also decrease their own sense of helplessness.

In line with the results reported by Hilgard and LeBaron (1982) and Liossi and Hatira (1999, 2003), hypnotizability in the present research is strongly related to the magnitude of the therapeutic benefit in the EMLA + hypnosis group. As hypothesized by Barabasz and Barabasz (1992), this type of finding supports a specificity of action between hypnotic ability and the intervention. Less than perfect correlation between hypnotizability and therapeutic outcome underscores the fact that hypnotizability is only one of the factors that influences the therapeutic outcome.

Hypnosis has several attractive features. It is safe and does not produce adverse effects or drug interactions. An additional benefit is that it can be generalized to other distressing circumstances. The child who learns hypnosis for management of LPs may apply his or her skills for lessening the distress of bone marrow aspirations, venipunctures, or managing nausea from chemotherapy (Liossi, 2000). Moreover, the child who practices psychological techniques for pain control may achieve a sense of mastery over their pain that is additionally therapeutic.

In the future, studies of hypnosis and pharmacological interventions are needed to delineate how individual factors influence the efficacy of these interventions. Specifically, a careful examination of the impact of developmental level, cognitive skills, and sex as they mediate and moderate response to treatment will be an important direction for research. Moreover, researchers in the future should focus on the long-term efficacy of psychological interventions, not only throughout treatment but also to the effects on the psychological state of the child after recovery (Liossi, 2002).

Taken in combination, the data and methodological considerations of this investigation provide compelling experimental evidence for the analgesic effect of the combination of hypnosis with local anesthetic, and they support the clinical management guidelines introduced by the WHO. The next step is to bridge the gap between research studies, international guidelines, and daily clinical practice.

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