

Pain Control During Intrathecal Chemotherapy. A Randomized Study

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Sixty-seven patients with acute lymphoblastic leukemia or non-Hodgkins lymphoma seen at the King Khalid National Guard Hospital (KKNGH) between January and December 1999 were studied to determine the best method of controlling pain during the intrathecal injection of methotrexate.

The age of the patients ranged between 2 and 14 years. They were randomly divided into three groups. The first group consisted of 24 patients all above the age of 3 years. This group was offered psychotherapy as the sole measure to try and control their pain. A second group of 22 patients were given oral morphine and intranasal midazolam. The third group of 21 children received intravenous morphine and midazolam. Pain was assessed using three standard international pain assessment scales, the CHEOPS, VAS, and the Faces scales.

Results. There were no major complications. The group of patients who received intravenous morphine and midazolam scored lowest in the three scales and this was statistically significant at the p -value < 0.05 . **Conclusion.** Intravenous morphine and midazolam are safe and more effective in reducing pain during the intrathecal injection of methotrexate than psychotherapy alone or oral analgesia.

(Egypt.J.Psychiat., 2001, 24 : 127 - 135).

INTRODUCTION

Cancer pain originates in noxious physical pathology, but it is always modified by the mind (Mount, 1984). Sanders (1967) coined the term "total pain" to describe the all encompassing nature of intractable cancer pain and the need to assess and treat all of its components, physical, psychological, financial, interpersonal and spiritual (Cassell, 1982). It was noticed that the pain of fatal illness is doubly painful because it threatens us with death (Mount, 1976).

Studies of juvenile chronic arthritis suggest that with increasing age the children experience greater pain, not because there is an actual increase in noxious stimuli from the involved joints, but largely due to the increased negative effect in the older child (Beales, 1979).

The pain related to lumbar puncture is mainly caused by the puncture of the skin and subcutaneous tissues by the spinal needle. Although the dura is a pain sensitive structure, it is uncommon for patients to experience pain as the dura is punctured or as intrathecal medication is instilled (Mc Garth & Mc Alpine, 1993). Although fear is commonly noted in children who are about to undergo painful medical procedures, surprisingly little research

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has focused on the measurement of medical fears (Zeltzer et al., 1997). Bone marrow aspiration, lumbar puncture, and intrathecal chemotherapy are the commonest sources of anxiety and pain in the pediatric oncology population. Yet these procedures are often performed without the benefit of a sedative, analgesic, or other coping strategy. Hypnosis, relaxation and other cognitive behavioral techniques can be extremely important adjuncts to pharmacological pain management in this setting (Ganea & Bogue, 1999; Kuttner et al., 1988).

The aim of this study was to compare three different methods of pain prevention prior to intrathecal therapy: psychotherapy, oral morphine plus intranasal midazolam (PO/IN), intravenous morphine plus intravenous midazolam (IV/IV).

SUBJECTS AND METHOD

Patients aged 2-14 years, with a diagnosis of acute lymphoblastic leukemia (ALL) or non-Hodgkin lymphoma (NHL) who were receiving intrathecal chemotherapy as part of their treatment at the King Khalid National Guard Hospital (KKNHG) were entered onto the study. Informed consent was obtained from the parents, the patients or both. Patients were randomized to one of three therapies. One group received psychotherapy by using simple teaching of the procedure of intrathecal injection (ITI), reassurance, modelling, rehearsal, telling stories, and hypnosis. Older children were subjected to cognitive behavioral therapy in the form of self-hypnosis, relaxation and thought stopping for negative thoughts about ITI. There were 3-5 psychotherapy sessions before the ITI and during the procedure itself (Zeltzer et al., 1989).

These sessions of psychotherapy were done by a well trained psychologist. Another group of children was given oral morphine in a dose of 0.2mg/kg 45 minutes before ITI in addition to intranasal midazolam 0.2 mg/kg 15 minutes before ITI. The third group of children received IV morphine 0.1mg/kg plus IV midazolam 0.1mg/kg three minutes before ITI. Precautions were considered towards the side effects of morphine & midazolam. ABC measures for shock were available in the room of ITI. Appropriate doses of naloxone and flumazenil-antidotes of morphine and midazolam- were available in the room of ITI. All patients had IV access at the time of pain assessment. No significant side effects of sedation analgesia were reported in this study for all patients who had been given morphine and midazolam. Pain was assessed by a psychiatrist (MS) during ITI using three different scales for each child to cover all ages of children in this study. The assessor of pain was blinded to the intervention that each patient received.

The first scale was a ten cm. Visual Analogue Scale (VAS). One end of the line was defined as ...very calm, very relaxed and the other end as ...very upset, very distressed. The psychiatrist marked the line at a point corresponding to how he felt about the child's feelings and behavior during ITI. The psychiatrist also rated how he thought the child felt immediately before having the needle, using VAS defined with the same grading (Abu-Saad, 1984). The second scale, the Childrens Hospital of Eastern Ontario Pain Scale (CHEOPS) was used to measure the behavioral distress during ITI. The CHEOPS is a time sampling behavioral pain scale developed for the measurement of post-operative pain in young children. It has been shown to have excellent inter rater reliability and

good validity. The behaviors are separated into 6 categories: cry, facial expression, verbal complaints, torso movement, touching, and leg movements. Behaviors are assigned a score value ranging from zero (the antithesis of pain) to three. The totals from each category are assumed to a global score ranging from 5-13 (McGarth et al., 1985; McGarth & Unruh, 1987; Aradine et al., 1988). The third method was the three Faces scale. It consists of a series of 6 pictures (fig 1). Several studies have reported good psychometric properties for this scale (Beyer & Aradine, 1987). All patients had pulse monitors for two minutes prior to ITI until two minutes after ITI was completed as a method of measuring the physiological response to pain (Beyer & Strada, 1986).

Statistical methods

All statistical analyses were performed using SPSS-PC+ package. The data were expressed as mean values SD, and a p value of < 0.05 was considered to be statistically significant (Norusis, 1986). Kruskal Wallis formula was used to compare between more than 2 means, while Mann Whitney was used to compare between 2 means (Kirkwood, 1988). Correlation

coefficients were measured for score values of different scales.

RESULTS

Sixty-seven patients were entered onto the study. There were 35 males and 32 females. Twenty-four patients were randomized to psychotherapy, 22 to PO/IN and 21 IV/IV. The characteristics of the 67 patients are shown in table 1. The three groups were not statistically different with regard to sex and age distribution. The duration of chemotherapy before enrollment into the study was longer in the psychotherapy group ($p = 0.001$). One patient allocated to the PO/IN group had trisomy 21. The correlation between the different scores of pain scales (CHEOPS, VAS, Faces) exceeded 90% as shown in table 2. Nineteen patients cried before the introduction of ITI needle. Their scores of pain were significantly higher than those who did not cry (table 3). Pulse rate before ITI was lower in the psychotherapy group, the difference between the three means before & after ITI was statistically significant ($p = 0.013$ & paired $t = 2.55$). The difference in pulse rate before and after

Table 1
Different Variables in the 3 Groups of the Study

	Psychotherapy	PO morphine IN midazolam	IV morphine IV midazolam	Significance
Number	24	22	21	
Sex male	12	11	12	
Female	12	11	9	
Age (years)	7.3 ± 3.1	6.5 ± 3	6.5 ± 3.8	$P = 0.56$
Duration of therapy wks	57 ± 36	28 ± 33	27 ± 33	$P = 0.001$

Level of significance where p is < 0.05

Table 2
Correlation between the Scores of Pain Scales

	Cheops	VAS	Faces
Cheops	1	.92*	.92*
VAS	.92*	1	.91*
	p<.00001		p<.0001
Faces	.90	.91*	1
	p<.0001	p<.0001	

Level of significance where p is <0.05

Table 3
Pain Scores of Those Who Cried Before ITI vs. Those Who Did Not Cry

	Cried before ITI	Did not cry before ITI	Z-test	Significance
Number	19	48		
Cheops	12.63±5.34	9.90 ± 3.79	-1.99	p = 0.040
VAS	5.84±2.69	3.52 ± 2.48	- 3.00	p = 0.003
Faces	3.52±1.58	2.65 ± 1.56	- 2.05	p = 0.040

Level of significance where p is <0.05

Table 4
Comparison of Psychotherapy, PO/IN, IV/IV groups as Regards to Pulse Rate and the Means of Pain Scales Scores

	Psychotherapy	POmorphine IN midazolam	IV morphine IV midazolam	Level of significance
Number	24	22	21	
Pulse before ITI	105±18	111 ± 21	120 ± 27	Paired-t = 2.55
Pulse after ITI	108 ± 16	125 ± 24	124 ± 28	p = 0.013*
CHEOPS	1106±4.7	12.7 ± 4.1	7.2 ± 2.3	p = 0.002*
VAS	4.8 ± 2.9	5.5 ± 2.5	2.2 ± 1.6	p = 0.0002*
Faces	3.2 ± 1.7	3.7 ± 1.2	1.7 ± 1.2	p = 0.0001*

* Level of significance where p is <0.05

Table 5
Distribution of Age, Sex and Type of Illnesses in both Groups of the Study

	Group of cancer	Group of Chronic illnesses	Significance
Age	50.1 ± 2.39	44.3 ± 3	t-test = 0.14
(mean ± SD)		20 / 10	χ ² = .63
Sex : F/M	17/13		p = .43
Type of illness:			
- CA breast	: 9 (30%)	- Diabetes :	10 (33.3%)
- CA GIT	: 10 (53.3%)	- Chest :	13 (43.3%)
- Other types	: 11 (36.9%)	- Other Illness :	7 (23.3%)
- total (no.)	: 3 (100%)	- Total :	30 (100%)

Level of significance p < 0.05

Ca : Cancer, GIT : Gastrointestinal Tract

Table 6
Mean Values & Standard Deviation of Hamilton Depression, Anxiety and Quality of Life for the most Attendant Caregivers in Both Groups of the Study

	Group of cancer	Group of Chronic illnesses	Significance
Age	50.1 ± 2.39	44.3 ± 3	t-test = 0.14
(mean ± SD)		20 / 10	χ ² = .63
Sex : F/M	17/13		p = .43
Type of illness:			
- CA breast	: 9 (30%)	- Diabetes :	10 (33.3%)
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Table 6
Mean Values & Standard Deviation of Hamilton Depression, Anxiety and Quality of Life for the most Attendant Caregivers in both Groups of the Study

	Hamilton anxiety	Hamilton depression	Physical QOL	Psychological QOL	Social QOL	Spiritual QOL	Total QOL
Hamilton anxiety	1.000 P = 0	0.81 p = .00*	0.48 p = .00*	0.47 p = .00*	0.72 p = .00*	0.42 p = .00*	0.50 p = .00*
Hamilton depression	0.81 P = .00*	1.000 P = 0	0.38 p = .00*	0.39 p = .00*	0.43 p = .00*	0.4 p = .00*	0.44 p = .00*
Physical QOL	0.48 P = .00*	0.38 p = .00*	1.000 p = 0	0.87 p = .00*	0.65 p = .00*	0.57 p = .00*	0.89 p = .00*
Psychological QOL	0.47 P = .00*	0.39 p = .00*	0.87 p = .00*	1.000 p = 0	0.81 p = .00*	.62 p = .00*	.92 p = .00*
Social QOL	0.47 p = .00*	0.43 p = .00*	0.65 p = .00*	0.81 p = .00*	1.000 p = 0	0.50 p = .00*	.86 p = .00*
Spiritual QOL	0.42 p = .00*	0.40 p = .00*	0.57 p = .00*	0.62 p = .00*	0.50 p = .00*	1.000 p = 0	0.70 p = .00*
Total QOL	0.5 p = .00*	0.44 p = .00*	0.90 p = .00*	0.95 p = .00*	0.86 p = .00*	0.70 p = .00*	1.000 p = 0

Level of significance p < 0.05

QOL : Quality of life for the most attendant caregiver

ITI for each group was not statistically significant ($p = 0.37$ and 0.59), except for PO/IN where paired t was 4.15 & $p < 0.001$.

Kruskal Wallis test for analysis of variance showed significant difference between the three groups of study with regard to CHEOPS, VAS, and Faces ($p = 0.0002, 0.0002, 0.0001$) respectively (Table 4). Further analysis with Mann Whitney test revealed no difference of CHEOPS, VAS and Faces between the psychotherapy group and PO/IN group ($p = .31, .46, \text{ and } .55$) respectively. Pain scores of the IV/IV group were significantly lower than the other two groups.

DISCUSSION

Childrens' pain may be undertreated for a number of complex and interacting reasons (Schechter, 1989). One major misconception is that children experience less pain because of neurologic immaturity. Another incorrect assumption is that children metabolize analgesics differently from adults (Maeks & Sachar, 1973). Others suggest that children have no memory of pain. Behavioral changes such as feeding, sleeping, and state control have been documented after painful procedures providing evidence that pain is remembered (Marshall et al., 1980). Others suggest that children might easily become addicted to narcotic analgesics, which is also incorrect. (Jaffe, 1985). In the past there was a great deal of concern regarding anticipatory pain in children. This resulted in the practice of undertaking painful procedures as quickly and expeditiously as possible. The development of topical analgesics and better short acting sedatives has changed this practice. Most institutions

now premedicate children prior to Lumbar punctures and other painful procedures.

Emlaream, a topical analgesic often used prior to ITI is not readily available at the KKNHG. We therefore evaluated three methods of providing pain relief from ITI: psychotherapy, oral or intravenous analgesia.

Childrens emotional reaction to medical procedures like ITI varies widely; some children begin crying loudly as the doctor cleans the skin for ITI, others sit stoically. In the present study, children who were crying before ITI had significantly higher pain scores. The factors that determine the nature and intensity of childrens reactions are not well understood. Parental attitude and emotional state can affect the child behavior through the following: facial expression & behavior of the parents, parental anxiety and depression, lack of parental support for their children during periods of extreme stress, and/or lacking the requisite parenting skills (Redd, 1994). We used VAS, CHEOPS and Faces to assess the degree of pain. The correlation between the three scale scores, which were used in this study, was more than 90%. This shows the efficiency of these scales in the assessment of pain before and after ITI.

The dose of oral morphine used in this study was one that was in common practice at the time. This dose is probably sub-optimal (Kennedy & Luhmann, 1999; Carr et al., 1992) and may account for the superior results of the IV/IV regimen. There were no significant side effects from the morphine and midazolam.

In this study, different methods of psychotherapy either behavioral, cognitive or even simple teaching of the procedure of ITI were used to reduce the pain scores during ITI. We did not

utilize a control group as this was regarded unethical. Moreover, psychotherapy as a method of pain relief before ITI was mentioned in a number of studies (Kuttner, 1989; Kuttner, 1993; Schanberg et al., 1997). Psychotherapy techniques can be chosen according to the child's age (Tendrup, 1996). Although the IV/IV proved superior to psychotherapy this does not mean that psychotherapy before and during ITI is not effective. Psychotherapy can be used as a synergistic or additive effect to intravenous use of morphine and midazolam for ITI.

The mean age of the psychotherapy group was higher than that of other two groups. It is well known that the older age children suffer from pain more than the younger age groups. This is due to anticipatory pain, which occurs following painful experiences. It is worth noting that the psychotherapy group had been on treatment significantly longer. The number of times these patients had received ITI was greater than for the other patients and therefore their anticipatory pain may be greater. The differences between pulse rates before and after ITI were not statistically significant for psychotherapy and IV/IV. Many factors can affect the pulse rate such as the drugs used in sedation/analgesia, age, and the physical condition of the child and anticipatory pain effect (Jay et al., 1985; Mathe & Mackie, 1983).

Conclusions

The methods of VAS, CHEOPS, and Faces scale are useful, reliable and reproducible tools to evaluate pain in children. The combination of all three methods permits pain studies to be undertaken in children.

Psychotherapy is as effective as oral morphine and intranasal midazolam but

less than intravenous morphine and midazolam. Adequate dosage of sedatives and analgesics must be given before painful procedures in order to prevent significant pain. The pulse is not a sensitive or specific physiologic method to measure pain. Further studies are needed to evaluate whether psychotherapy has an additive effect.

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التحكم فى الألم أثناء حقن النخاع الشوكى بالعلاج الكيماوى دراسة عشوائية

تم إجراء هذه الدراسة على ٦٧ مريضاً، وكان الغرض منها هو تحديد أفضل طريقة للتحكم فى الألم أثناء حقن النخاع الشوكى بالميثوتريكسات للأطفال المصابين بلوكيميا ليمفاوية حادة أو مرض الليمفوما بمستشفى الملك خالد للحرس الوطنى، فى الفترة من يناير وحتى ديسمبر ١٩٩٩ وقد تراوحت أعمار المرضى فى هذه الدراسة من ٢ - ١٤ عاماً. حيث تم تقسيمهم عشوائياً إلى ثلاث مجموعات :

المجموعة الأولى تكونت من ٢٤ مريضاً عمرهم جميعاً أكثر من ثلاث سنوات، وقد خضعوا جميعاً للعلاج النفسى كوسيلة وحيدة للتحكم بالألم. المجموعة الثانية تكونت من ٢٢ مريضاً أعطوا المورفين بالفم، والميدازولام عن طريق الأنف. أما المجموعة الثالثة فتكونت من ٢١ طفلاً، أعطوا نفس العقارين السابقين عن طريق الوريد. وقد تم قياس درجة الألم أثناء الحقن النخاعى بالميثوتريكسات عن طريق استخدام ثلاثة مقاييس مقننة عالمياً لقياس درجة الألم؛ ولم يكن هناك مضاعفات لاستخدام هذه العقاقير للتحكم فى الألم. وقد وجد أن المجموعة التى خضعت للعلاج الوريدي هى أقل المجموعات الثلاث إحساساً بالألم بدرجة ذات دلالة إحصائية "قيمة ب > ٠,٠٥". نستنتج من هذه الدراسة أن استخدام عقارى المورفين والميدازولام بالوريد للتحكم فى الألم قبل حقن النخاع الشوكى بالميثوتريكسات أكثر فاعلية من المورفين بالفم والميدازولام بالأنف والعلاج النفسى بطرقه المختلفة.