Int. J. Radiation Oncology Biol. Phys., Vol. 49, No. 3, pp. 771–783, 2001

0360-3016/01/$–see front matter

PII S0360-3016(00)01357-2

CLINICAL INVESTIGATION **Pediatrics**

EVALUATION OF THE SAFETY AND EFFICACY OF REPEATED SEDATIONS FOR THE RADIOTHERAPY OF YOUNG CHILDREN WITH CANCER: A PROSPECTIVE STUDY OF 1033 CONSECUTIVE SEDATIONS

GAIL SEILER, A.S.R. (R) (T),* EDWARD DE VOL, PH.D.,† YASSER KHAFAGA, M.D.,‡ BRIAN GREGORY, M.D.,§ MOHAMMAD AL-SHABANAH, M.B.B.S, F.R.C.P. (C),‡ ADELA VALMORES, R.N.,* DEBORAH VERSTEEG, R.N.,* BARBARA ELLIS, D.C.R.T.,* MAHMOUD M. MUSTAFA, M.D.,‡ AND ALAN GRAY, F.R.A.C.P., F.R.A.C.R.‡

Departments of *Radiation Therapy, †Biomedical Statistics, ‡Oncology, and §Anesthesiology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Purpose: A prospective observational study to examine our current practice of either conscious sedation (C.S.) or general anesthetic (G.A.) for children undergoing radiation therapy (we use the term sedation to include both C.S. and G.A.). Specifically, the study examines the reasons for selection of patients, choice of drugs, safety and effectiveness of the procedure, side effects of repeated daily sedation, and compliance of the family with the regimen.

Methods and Materials: Recorded data included patient demographics, sedation technique, time for various stages of the procedure, breathing support required, sedation outcome, and complications.

Results: One hundred ninety-eight consecutive children underwent 4232 procedures involving either simulation or radiation treatment, an average of 21 procedures each. Seventy-four (37%) required sedation for a total of 1033 procedures, an average of 14 sedations each. For those patients who received sedation, the age ranged from 9 months to 14 years (median, 3.8) and 96% had a mold, (85% of the head and neck). The doctor's assessment of the need for sedation was correct 89% of the time. Thirty-seven percent required sedation at the start of treatment, but, even after 30 fractions, 15% still required sedation. Presedation status correlated with successful sedation and treatment ($p = 0.0001$). Ninety-six percent had some form of i.v. access, usually a portacath (76%); 883 sedations were performed with G.A. and 148 with C.S.; 93% of sedations were completed satisfactorily, 5% with some difficulty, and the patient was unable to be treated in 2%. With G.A., satisfactory sedation was achieved 97% of the time, whereas, with C.S., satisfactory sedation was achieved only 68% of the time. There were no complications for 97% of observations. Not one serious complication occurred. An endotracheal tube was used only twice during G.A. For C.S., the results for chloral hydrate, meperidine, and midazolam were, respectively, at least one complication, 23%, 0%, 5%; satisfactory sedation for treatment, 60%, 60%, 82%; and unable to treat 20%, 13%, 5%. For G.A., only 1 patient was unable to be treated. The median time from start of medication to the end of radiation treatment was a median of 10 min (75% complete within 15 min) for G.A., vs. 30 min (75% complete in 50 min) for C.S. On multivariate analysis, the only significant factor predicting a successful outcome was a G.A. using propofol (odds ratio, 20.6), vs. C.S. using either chloral hydrate, meperidine, or midazolam. ($p = 0.0001$).

Conclusion: In this study, there were no serious complications of sedation in 1033 procedures. As a result of the study, we developed improved methods for better preparation of the patient and family to try to reduce the need for sedation, and reduce the indications for C.S., while confirming the safety and efficacy of a G.A. with propofol for children needing sedation for daily radiation therapy. © 2001 Elsevier Science Inc.

Childhood cancer, Radiation therapy, Conscious sedation, Anesthesia, Propofol.

INTRODUCTION

Radiation therapy is one of the most accurate treatments in medicine, but its therapeutic margin of safety in cancer treatment is low. Underdosage of a tumor by either reduced radiation dose, or geographic miss of part of the tumor, results in treatment failure. Conversely, increased radiation dose or treating too large a volume may result in unacceptable complications. These risks are compounded in children, who are particularly susceptible to effects, such as delayed growth, neurologic dysfunction, or endocrine disturbance in future years. In Western

Reprint requests to: Dr. Alan Gray, Department of Oncology, MBC64, King Faisal Specialist Hospital and Research Center, P.O. Box 3354, Riyadh 11211, Saudi Arabia. E-mail: agray@kfshrc.edu.sa

All resources for this study were provided by King Faisal Specialist Hospital and Research Center. No other funding or support was either requested or received.

Accepted for publication 14 March 2000.

studies, 60% or more of children with cancer now survive long term, and the late effects of treatment are a real area of concern (1).

To minimize complications and improve results, many children require immobilization, usually with the aid of individually molded plastic shells. The most common area to be immobilized is the head and neck, for either brain or head and neck tumors, and patients may have to lie either supine or prone. For young or anxious children, this can be an intolerable experience, to lie for 10–20 min with their head or body in a cast. Sedation is, therefore, an essential part of pediatric radiation therapy practice.

Reports in the literature record the potential consequences of inadequate immobilization. Jereb *et al.* (2) recorded an unacceptably high rate of failure in children treated for medulloblastoma in the region of the cribriform plate, an area very sensitive to changes in position because it limits the required shielding of the eyes from radiation. This was confirmed by a study from the French Society of Pediatric Oncology, who found 5 relapses in the frontal region of the brain in patients with major deviation in this area (3). McCormick *et al.* (4) reported a high rate of normal tissue damage with cataract formation and a high tumor failure rate, when unanesthetized children were treated for retinoblastoma of the eye, which is also technically a precise and demanding treatment.

Fifteen percent of all cancer patients referred to King Faisal Specialist Hospital and Research Center (KFSH & RC) are children (defined as age 14 years or younger), and the Section of Radiation Oncology averages 14 children per day undergoing radiation therapy treatment.

Although local attempts have been made to develop a hospital-wide protocol for sedation of children for procedures, such guidelines mainly apply to single procedures; and sedation for radiotherapy as a repetitive procedure, 5 days a week for several weeks, usually on an outpatient basis, has its own hazards. The effect of repeated sedation on nutritional intake and performance status can be exacerbated by the malaise and anorexia induced by radiotherapy. This can be further compounded by the effect of concomitant cytotoxic chemotherapy, which these patients also frequently receive. Although there are explicit guidelines produced by the American Academy of Pediatrics for safe sedation (5), they also refer particularly to single procedures. When this study commenced, there was no large series on the safety and effectiveness of repeated sedations or anesthesia during radiation therapy, and not a lot of general literature on the subject (6–15).

Since 1992, our department has been refining its protocol for the safe and effective sedation of children. This prospective observational study examined current practice in detail: the reasons for selection of patients, choice of drugs, safety and effectiveness of the procedure, side effects of repeated daily sedation or anesthesia, and compliance of the family with the regimen.

METHODS AND MATERIALS

From September 1996 until January 1998, a total of 198 pediatric patients presented for radiation therapy and were registered for this study.

Definition of terms

Pediatric patient: Patient 14 years of age or less.

Conscious sedation (C.S.): A medically controlled state of depressed consciousness that (*1*) allows protective reflexes to be maintained; (*2*) retains the patient's ability to maintain a patent airway independently and continuously; and (*3*) permits appropriate response by the patient to physical stimulation or verbal command, e.g., "open your eyes" (5).

General anesthesia (G.A.): A medically controlled state of unconsciousness, usually accompanied by a loss of protective reflexes, including the inability to maintain a patent airway independently, and respond purposefully to physical stimulation or verbal command (5).

Sedation: For the purposes of this paper, the generic term sedation can refer to either conscious sedation or a general anesthetic.

Objectives

1. To ensure the safety and welfare of the patient.
2. To evaluate our predetermined criteria for selection of patients for sedation.
3. To evaluate the effectiveness of various forms of sedation in allowing radiotherapy to be performed on the patient.
4. The ability to return the patient to a state in which safe discharge is possible.
5. The effect of sedation on the patient's nutrition during the course of radiation therapy.
6. The ability of the family to comply with a sedation regimen.

Eligibility

Selection. All pediatric patients who were to receive a course of radiation therapy at KFSH & RC during the study period were registered, so that the study gives an account of the total population as well as the subpopulation receiving sedation.

Informed consent. All patients had a signed informed consent form for treatment from a responsible family member, which included consent for either C.S. or G.A., if required. The type of sedation given was not randomized. The study was approved by the Research Advisory Council of KFSH & RC and its Ethics Committee.

Adverse reactions. There had to be no history of adverse reaction to any of the drugs used in this protocol that were likely to be applied to the patient.

Health evaluation. There had to be no absolute medical contraindication to sedation.

Procedure

Information recorded at registration included patient's age, gender, weight, height, diagnosis, allergies, other significant illnesses, the length of the proposed course of radiotherapy, number of treatment fields, the treatment position, and the need for a mold.

An assessment of the need for sedation was made at the time of the initial visit with the radiation oncologist, which was also the time of registration for the study. Factors considered in this assessment were patient's age, emotional maturity, anxiety, ability to cope with previous treatments or investigations which required compliance, e.g., CT scans; and the complexity of the proposed radiation treatment itself, e.g., treatment in the prone position, which is more difficult for the child. Family and staff who knew the child were consulted.

In addition, diagnosis was a further consideration: patients with a diagnosis of intraocular retinoblastoma to be treated with curative intent all received a G.A. with propofol to ensure that the patient's eye remained stable and neutral with the lens anteriorly throughout the procedure so that a lens-sparing technique could be used (16).

Once accepted for treatment, the patient and caregivers were instructed further on their radiation therapy by an Arabic-speaking nurse. For patients receiving sedation, families were provided printed instructions in Arabic for "nil by mouth" (n.p.o.) status, and were counseled on the importance of complying with these guidelines. These were (*1*) no solid food for 4 h before treatment; and (*2*) no liquids or anything by mouth for 2 h before treatment, including breast milk (17).

Patients undergoing sedation were scheduled to arrive 1 h before the actual treatment time. Their pulse, temperature, respiratory rate, blood pressure, and oxygen (O_2) saturation were recorded. Their general condition and i.v. line (if present) were checked. n.p.o. status was confirmed and documented by the nurse.

The sedation room was equipped with the following: oxygen, suction, blood pressure apparatus, pulse oximeter, and the emergency medical supplies cart ("crash cart"). The environment was made suitable for patients receiving sedation: a darkened room with quiet surroundings were provided, and the patient and family were reassured. Mothers were encouraged to remain with their child throughout the sedation procedure until the child was actually treated.

Before medicating the patient (or immediately following if the child was distressed), the pulse oximeter was attached to the patient for continuous monitoring until eventual discharge. Patients were made comfortable (positioned on their side, or small children remained on mother's lap). Bed rails were raised for safety.

A registered nurse remained with sedated patients continuously to ensure their safety, for continuous monitoring, and to note retention of oral (p.o.) or rectal (p.r.) medications. Pulse, respiration, and oxygen saturation readings were recorded at 15-min intervals or more often as necessary.

The final decision on whether the child was to receive either C.S. and with which drugs, or a G.A. was decided by the radiation oncologist. There were no clear guidelines in the literature on the choice or route of drugs (18), and so based on previous experience in the department, the following list of medications were selected from which the oncologist could choose according to his experience and estimate of the patient's need. It was understood from the beginning of this study that preference for particular drugs and the choice of either C.S. or G.A. could change as experience was gained.

For molding and simulation, the patients initially received C.S. rather than a G.A. (with the exception of retinoblastoma as explained above). G.A. was intended to be used only if C.S. was ineffective. The mold and simulation procedures were to serve as a preliminary assessment of the effectiveness of the following drugs for C.S.:

1. Chloral hydrate of 75–100 mg/kg p.o. or p.r. If adequate sedation was not achieved in 20 min, a second dose of 25 mg/kg could be given if the lesser dose of 75 mg/kg was used initially. The maximum dose was not to exceed 2000 mg.
2. Midazolam of 0.05–0.2 mg/kg given by slow i.v. push over 3–5 min, and titrated to effect. It was recommended to give oxygen by mask during the procedure. (Oral and intranasal midazolam (19) was tested on a few patients before this study, but appeared unreliable, and its use was abandoned before the study began).
3. Meperidine (demerol/pethidine) of 0.5–1.0 mg/kg, maximum 20 mg, to be given by slow i.v. push over 3–5 min.

An order for the sedation was recorded in the medical record by the oncologist. The medication for C.S. was administered by a senior staff nurse, who monitored the process, and remained present for the duration of C.S. until the patient was discharged. These nurses were previously orientated in the hospital's main operating theater recovery room, which was followed by a competency check-off. Antidotes of flumazenil, the benzodiazepine antagonist, and naloxone the narcotic antagonist were always present and available. Patients continued to be assessed during the first five treatments of radiation therapy using chloral hydrate, midazolam, or meperidine only. Patients proceeded to G.A. administered by a consultant anesthetist if regular "boosting" of chloral hydrate was required; the sedation was not satisfactory, i.e., child was not ready for treatment within 30 min; if, after 5 treatments, they were still requiring more than 75 mg/kg of chloral hydrate alone daily, as this drug has a long recovery time and there was concern that these children would suffer from lack of nutrition and hydration by its prolonged use in higher doses.

For patients who received a G.A., the medication used was at the discretion of the anesthetist, but they were encouraged to use propofol, which was still a relatively new drug for use in children in this hospital at the beginning of this study. The Anesthetic Department provided a rotating

roster of anesthetists to provide comprehensive coverage starting at 8 am each working day.

Following radiotherapy treatment, the patient was transported to the recovery room still under monitoring. Inpatients were transferred back to the ward after a minimum of 45 min in the recovery area, accompanied by a nurse who transferred the care to the ward nurse. For outpatients the discharge criteria were (*1*) alert and orientated; (*2*) vital signs stable for 30 min, and minimal nausea and no vomiting; (*3*) ambulates with minimal assistance (if appropriate); (*4*) after a minimum of 1 h in the recovery area.

Parents were instructed to bring the child to the department, or to the emergency room outside of working hours, if there was any concern about the child's status.

Completion of an evaluation form each day was the responsibility of nursing staff, whether the child had C.S. or G.A. Eight separate items were monitored and recorded with each sedation. The overall sedation result was recorded as one of three categories: (*1*) Satisfactory, treatment completed without difficulty; (*2*) Treatment completed but with some difficulty; or (*3*) Unable to be treated.

The specific outcomes which the study was intended to measure included (*1*) the length of time for various stages of the procedure from start of sedation medication, through treatment, to time of discharge; (*2*) whether breathing support, (i.e., airway support) was required; (*3*) whether a satisfactory level of sedation was achieved which allowed radiation therapy treatment to be given; and (*4*) whether any complications occurred as a result of administering sedation.

These outcomes were to serve as critical success factors.

Statistics

This is an observational study, covering every pediatric patient presenting for radiation therapy during the recruitment period of September 1996 through January 1998. The population to which inferences are made is that group of children with cancer who may be treated with radiation therapy at the King Faisal Specialist Hospital and Research Center. The inferential population is likely to be similar to all such children, because the referral patterns do not vary across societal subgroups.

The study included two forms—a so-called registration form and a so-called evaluation form. The former was used to record basic demographic information on each patient entered into the study, be it a patient who subsequently received sedation during his/her treatment or not. The evaluation form was used to record information on patients during an episode of treatment (or simulation/mold) when sedation (C.S. or G.A.) was administered. The form allowed the recording of some basic information about the patient upon arrival to the radiation therapy unit, as well as the recording of information particular to the administration of the sedation (e.g., who administered, time administered, route, type of drug, etc.).

The statistical computing was done using SAS version 6.10 on a DEC Alpha system running OpenVMS. The data entry and management had been done in the SIR database program.

The analysis was divided into five parts. The first part entailed a summary of the study patients in terms of basic demographic information, the types of their diseases, how they were treated with radiation therapy (e.g., number of procedures, position, etc.), how they were sedated and whether their treatment procedure was successful. The second part described the information recorded during the treatment procedure, e.g., types of sedation, complications, etc. The third part described variables that are associated with the various types of sedation, e.g., demographic information, treatment information, complications, and successful treatment. The fourth part involved the analysis of information over time, both across procedures for individual patients and within a procedure from the time of administration of sedation to discharge from the department. The final part analyzed the success of treatment and the extent to which it may be related to various factors for which information was recorded.

Nonparametric statistical techniques were employed for the most part, with the exception of a logistic regression. A p value of 0.01 was employed for threshold statistical significance—adjusting for the number of tests carried out.

RESULTS

All patients

A total of 198 children were registered. Five patients did not proceed to radiation therapy because of a change in their status between their first assessment and their planning appointment, so 193 actually received radiation therapy, for a total of 4232 procedures involving molding, simulation, and radiation treatment, an average of 22 procedures each.

There were 111 male and 87 female (M:F ratio = 1.3:1). Age ranged from 5 months to 14 years, with a median of 7 years. ECOG performance status was 0/46 (28%), 1/73 (37%), 2/17 (9%), 3/28 (14%), 4/24 (12%), respectively. Thus, 26% of patients had an impaired performance status of 3 or 4. A total of 152 (79%) were treated supine, and 41 (21%) were treated prone. A total of 167 children (87%) had a mold for treatment. Of these, 147 (76%) had a mold of the head and neck, 8 (4%) had a chest mold, 14 (7%) had an abdominal mold, and 5 (3%) had a limb molded. Two other patients had total body irradiation surrounded by packing with rice bags. The number of radiation fields planned for each patient were, respectively: 1/14 (7%), 2/122 (61%), 3/51 (26%), and 4/11 (6%). Mold and simulation episodes were added as 2 treatments to each patient's course. The median number of treatments given was 20 (range, 1–35). The list of diagnoses is given in Table 1. One-third of all patients had brain tumors. All patients were treated on linear accelerators with photons (6 or 18 MV) or electrons.

Sedated patients

Seventy-four (37%) required sedation for a total of 1033 procedures, an average of 14 sedations each. For compari-

Table 1. Diagnosis of 198 children referred for radiation therapy

Diagnosis	Frequency	Percent
Leukemia	51	25.8
Lymphoma	15	7.6
Neuroblastoma	3	1.5
CNS tumors	65	32.8
Astrocytoma	9	4.5
Medulloblastoma	23	11.6
Other	33	16.7
Retinoblastoma	17	8.6
Wilms	10	5.1
Ewings	10	5.1
Rhadomyosarcoma	10	5.1
Soft tissue sarcoma	2	1.0
Fanconi's anemia	5	2.6
Other	10	5.3
Total	198	100%

CNS = central nervous system.

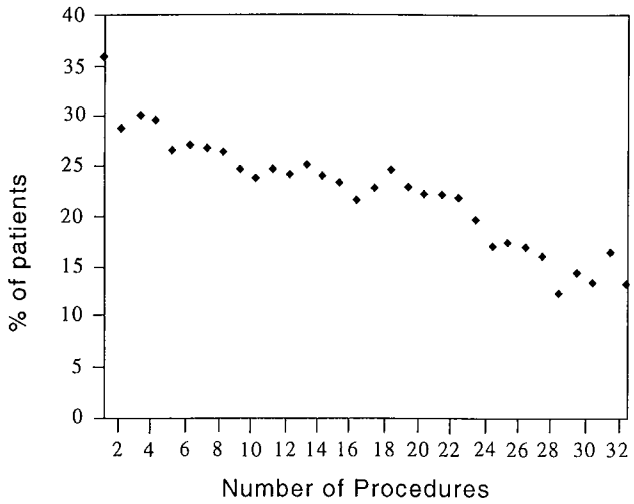

Fig. 1. Percentage of patients receiving radiation therapy who require sedation over time.

son between the sedated, and the nonsedated patients, we adjusted for sedation intensity, by dividing the number of sedations by the total number of treatments the patient received.

$$\text{Sedation intensity} = \frac{\text{number of sedations}}{\text{total number of treatments patient received}}$$

Age

The age of the sedated patients ranged from 9 months to 9 years (median, 3.8 years), vs. from 5 months to 14 years (median, 9 years) for nonsedated patients. Age was dichotomized into those less than 7 years, and those at least 7 years, and there was a significant relationship between the dichotomy and sedation ($p = 0.0001$), number of sedations ($p = 0.0001$), and sedation intensity ($p = 0.0001$) with the older group as expected being sedated less.

Molds

Seventy-one (96%) of the sedated patients had a mold, vs. 96 (77%) of nonsedated patients. On univariate analysis, this was significant for requiring sedation for head and neck molds only ($p = 0.001$).

Reasons for selection

The radiation oncologist had 5 choices as to why the patient was selected for sedation. These were young age, anxiety, treatment complexity, emotionally immature for age, and history of noncompliance. There were often multiple reasons for selecting sedation for each patient. There was no significant difference within these selection factors as to their accuracy for requiring sedation, and the number of sedations, but there was a marginal significance ($p = 0.04$) for young age for sedation intensity. Table 2 shows the number of patients, the type of sedation, and the reason for selecting sedation. Twenty percent of patients selected for sedation on the basis of anxiety did not require it.

Of the 198 patients, 73 were initially assessed as requiring sedation, and 86% of these received sedation. For the remaining 125 patients considered not requiring sedation, this was correct 91% of the time; 11 of the 125 subsequently requiring sedation. Overall, the initial assessment was correct 89% of the time.

Rate of sedation over time

Figure 1 shows the percentage of patients requiring sedation during their treatment course. Initially, 37% of all patients required sedation. The line-graph fluctuates, as

Table 2. Reasons for selection and type of sedation recommended

Type of sedation	Patients (%)	Young age	Immaturity	Anxiety	Noncompliance	Treatment complexity
Chloral hydrate p.o.	20 (27.4)	13	0	12	17	12
Chloral hydrate p.r.	2 (2.7)	1	0	0	1	2
Midazolam i.v.	14 (19.2)	5	0	8	8	10
Meperidine i.v.	11 (15.2)	3	2	8	9	8
General anesthetic	26 (35.6)	17	2	16	15	23
Total	79 (100.0)	39	4	44	50	55
Did not require sedation		10%	0%	20%	10%	9%

Note: Multiple answers = patients can have multiple reasons for sedation.

Table 3. Sedation requirements according to diagnosis

Diagnosis	No. of patients	Required sedation (%)	No. of sedations*	Sedation intensity†	Median age (years)	Molds (%)
Soft tissue sarcomas	13	62	12	10.4/20	4.8	92
Renal tumors	11	45	6	7/20	4.4	82
Leukemia	51	39	4	5.2/20	7.2	88
CNS tumors	67	37	5	3.2/20	7.7	96
Lymphoma	15	7	0	0/20	9.8	53
Ewings sarcoma	10	0	0	0/20	9.1	80
	Total = 167	$p = 0.008$	$p = 0.004$	$p = 0.003$		NS

CNS = central nervous system.
*Mean number of sedations.
†Sedation intensity = no. of sedations ÷ total no. of treatments; and refers to the mean number of sedations a patient with this tumor diagnosis could expect to receive if they were having 20 radiotherapy treatments.

some patients no longer require sedation, and other patients, after an uncertain start, proceed with sedation. Even after 32 treatments, however, 15% of patients still required sedation.

Tumor type

The 198 patients were separated by diagnosis into 5 common categories of tumor. Those with small numbers of a particular tumor type ($n = 31$) were excluded from this analysis. The 5 categories were leukemia, lymphoma (including Hodgkins), central nervous system (CNS) tumors, renal tumors, Ewing's sarcoma, and other sarcomas of soft tissues. There was a significant difference in the sedated population between sarcomas and lymphomas ($p = 0.008$). This was also significant for the number of sedations ($p = 0.004$) and for sedation intensity ($p = 0.003$). Table 3 lists the disease categories in descending order of sedation requirements and the results for each category, including median age and the percentage requiring molds. Age is obviously significant in deciding on sedation, but there was no significant difference in the requirement for molds to explain an association with tumor type.

The same diagnostic groups were analyzed using only those patients who were sedated, when there was no difference in the number of sedations or the sedation intensity between each disease group.

Gender

The gender distribution for sedated and nonsedated patients was identical; 56% male and 44% female.

Allergies

Three patients (1.5%) had a history of allergy to medications. Two patients did not require sedation, and the one who did had 27 consecutive sedations without incident.

Presedation status

The presedation status of the patient at each visit was compared with the ability to treat (see Table 4). For 82 procedures (8% of the total), the patients were recorded as being anxious/restless on arrival; 75% of these received satisfactory sedation for treatment, 14% were treated with some difficulty, and 7% were unable to be treated. In 949 procedures, the patient was considered calm/awake; 92% of these received satisfactory sedation, 5% with some difficulty, and 2% were unable to be treated. The difference was significant ($p = 0.0001$). Out of the total of 1033 sedations, a patient could not be treated on 18 occasions (2%).

Intravenous access (i.v.)

Seventy-one percent of the sedations were performed with a portacath in place, 19% with a heplock, 7% with a central line, 0.3% with a Hickmans catheter, and only 4% had no i.v. access. Portacath usage increased with the length of the treatment. At the start of treatment, 46% of sedations were performed with a portacath, rising to 94% by the 23rd sedation. Heplocks were used in 25% of patients at the beginning, peaked at 30% by the 3rd sedation, and, after 10 sedations, remained below 12%. Sixteen patients were sedated without i.v. access for a total of 38 sedations. Treatment was rated satisfactory 93% of the time with i.v. access,

Table 4. Presedation status and outcome of treatment

Patient's status	No.	Treated satisfactorily	Treated with some difficulty	Unable to treat
Anxious/restless	82	75%	14%	7%
Calm/awake	949	92%	5%	2%
Sleeping/responds to stimulus	1	100%	—	—
Unresponsive	0	—	—	—

Table 5. Type and mean dose of sedation used

Drug	No. of procedures	Mean dose/ procedure in mgs/kg
Propofol G.A.	837 (81%)	4.8
Meperidine C.S.	15 (1.5%)	0.92
Chloral hydrate C.S.	30 (3%)	100
Midazolam C.S.	78 (8%)	0.26
Other G.A.	46 (5%)	N/A
Other C.S.	25 (2.5%)	NA

Abbreviations: G.A. = general anesthetic; C.S. = conscious sedation.

but fell to 74% if there was no i.v. device available. On univariate analysis, patients with a portacath were more likely to have a satisfactory result (96%) than patients with a heplock (86%) ($p < 0.0001$).

Compliance

Forty-nine percent of the sedations were on inpatients, and 51% were on outpatients. The ability of patients and their parents to comply with the presedation regimen was monitored. The result was good 97% of the time, poor (patients were more than 30 min late for their appointment) in 3%, and poor (the patient was not n.p.o.) in only 4 sedations. On only one occasion was the patient both late and not n.p.o. There was no significant difference in compliance between inpatients and outpatients. Patient's age did not affect compliance.

Diagnosis and type of sedation

When the type of sedation is correlated with tumor diagnosis, patients with leukemia were more likely to receive a G.A. with propofol (87%) than Wilms' tumor (47%), who were more likely to receive C.S. particularly with midazolam (37%). This correlation was not related to age where the median age for leukemia was 7 years, and for Wilms' tumor 4.4 years, but to the use of a head and neck mold for the leukemias.

Type of sedation and results

A total of 883 sedations (86%) were performed with a G.A., and 148 (14%) were performed with C.S.; 93% of sedations were satisfactory, 5% were sedated with some difficulty, and in only 2% was the patient unable to be treated. With the use of a G.A., satisfactory sedation was achieved in 97%. C.S. gave a satisfactory result in only 68% which was significant ($p = 0.0001$). Only one G.A. was unable to be treated, a child brought for treatment not n.p.o. who began vomiting with induction, and the procedure was abandoned, and repeated later in the day when a satisfactory result was achieved. For detailed analysis of the medication given, those patients who received multiple medications for either G.A. or C.S. (a total of 71 sedations) were analyzed separately from those patients who received single agents consistent with the protocol (see Table 5).

Table 6. Complications of sedation

Complications	Number of observations	Incidence (%)
None	8221	98.7
Vomiting	18	0.2
BP < 30% baseline	1	0.0
O_2 sat < 90% > 15 sec	35	0.4
Pulse > 160	39	0.5
Apnea	13	0.2

BP = blood pressure.

Multiple daily fractions

Three patients had twice daily treatment, 6 h apart, for a total of 14 treatments using a propofol G.A.; 2 of these patients had 6 treatments each as part of their total body irradiation protocol for a bone marrow transplant. All treatments were completed satisfactorily without complications.

Drug dosages

The mean dose of drug given per procedure was calculated as follows: propofol, 4.8 (range, 1.5–28.2) mg/kg; meperidine, 0.92 (range, 0.69–1.11) mg/kg; chloral hydrate, 100 (range, 10–167) mg/kg; and midazolam, 0.26 (range, 0.07–0.65) mg/kg.

Analysis of the 837 sedations with propofol, showed no significant fluctuation in the dose used over time, up to 35 consecutive sedations. There was no evidence of developing tolerance to propofol.

Complications

Table 6 lists complications and, as these can be multiple within a single sedation, they are listed by the number of observations, a total of 8327. For 98.7% of the observations, there were no complications. Two patients with retinoblastoma, aged 3 years, 6 months, and 1 year, 8 months, who were being treated supine with a head mold and receiving a G.A., required an endotracheal tube on one occasion each of their 22 treatments, to maintain a patent airway. One was induced with ketamine followed by propofol, and the second received propofol only. Neither was considered a serious problem, and treatment was completed in each case. Otherwise, no largyngeal masks or endotracheal tubes were used or required. Among the 1033 sedations, not one serious complication occurred.

Table 7 lists the complications by type of sedation used and the result of treatment. Chloral hydrate was the least successful, with at least one complication occurring in 23% of sedations; in only 60% of sedations was the treatment considered satisfactory, and 20% of patients were unable to be treated. This was followed by meperidine, which had no significant complication rate, but only a 60% satisfactory treatment rate, and 13% were unable to be treated. Midazolam had a 5% complication rate, but, in 82% of patients, treatment was able to be completed satisfactorily, with only 5% unable to be treated.

Table 7. Complications according to type of sedation used

Type of sedation	No. of Procedures	Vomiting	BP less than 30% Baseline	O_2 saturation less than 90% for more than 15 sec	Pulse > 160 per minute	Respiratory rate less than 12	Apnea	No. of Complications*	% of sedations with at least 1 complication	Treatment satisfactory	Treatment difficulty	Unable to treat
Propofol	837	6	0	25	13	0	12	56	7%	98%	2%	1 patient
Chloral hydrate	30	4	0	0	3	0	0	7	23%	60%	20%	20%
Meperidine	15	0	0	0	0	0	0	0	0	60%	27%	13%
Midazolam	78	0	0	2	2	0	0	9	5%	82%	13%	5%
Other G.A.	47	1	1	5	1	0	1	9	17%	89%	11%	0
Other C.S.	25	2	0	0	2	0	0	4	12%	32%	48%	20%

Abbreviations: G.A. = general anesthetic; C.S. = conscious sedation; BP = blood pressure.
*Note that multiple complications are possible.

O_2 saturation was monitored continuously with a pulse oximeter and recorded regularly by the nurse. The median O_2 saturation was 98%. In 5% of the recordings, it fell to less than 81%, and in 1% of recordings it fell to less than 48%. The charts of these hypoxic patients were reviewed. There were no complications recorded in the anesthetic notes. Some of the very low levels may have reflected difficulties with the interface between the pulse oximeter and the patient.

Importantly, there was no significant difference in O_2 saturation between patients being treated in a supine or a prone position.

Airway and ventilation requirements were recorded, and 97.3% of patients underwent the procedure with spontaneous ventilation. Only 2.6% required a chin-lift. Ventilator assistance was used once (0.1%), and endotracheal intubation was used only twice, as mentioned previously. A total of 945 procedures resulted in a mask or nasal cannula being used at some point in time after starting the sedation. However, increasingly with G.A. or C.S, a mask or nasal cannula was used prophylactically. A total of 5 patients required assistance with an ambu bag (assisted ventilation) for a total of 8 episodes. On each occasion, the patient was becoming hypoxic with a falling oxygen saturation. Three of the 5 received a propofol G.A. In all cases, the sedation and treatment were completed, and none was considered an important complication (see Table 8 for details).

Fourteen patients developed sepsis while on radiation treatment. All 14 had received prior chemotherapy and presented with fever, which was associated with neutropenia in 11. A positive blood culture was found in 11. Four of the removed catheters also grew organisms. Pathogens cultured included coagulase negative *Staphylococci* (8), *Enterobacter cloacae* (3), *Pseudomonus aeruginosa* (2). Another patient was clinically septic, but blood cultures were negative, and he was treated as such with empiric antibiotics. At the time of infection, 8/14 patients had central venous access, 4 of which were infected and had to be removed or replaced. Eight of 14 (57%) were receiving a propofol G.A. at the time sepsis occurred. All septic episodes were successfully treated. Overall, 14/61 patients (23%) with central venous access developed sepsis.

Weight change

There were 54 patients for whom at least two weight measurements were available, and, on average, the weight change spanned 16 sedations. The average weight loss was 0.003 kg per sedation. Up to 10 sedations, there was a weight gain of 0.49 kg. (3.5% gain in average bodyweight [B.W.]) From 10 to 20 sedations, there was a weight loss of 0.92 kg (6.3% loss in B.W.). From 20 to 30 sedations, the loss was 0.18 kg (1.3% loss in B.W.), and for > 30 sedations the loss was 0.33 kg (2.4% loss in B.W.). There was no correlation of weight loss with age, being an inpatient or an outpatient, performance status, diagnosis, or type of sedation.

Table 8. Airway and ventilation requirements during sedation

Type of sedation	No. of procedures	Chin lift	Bagging	Ventilator	Mask/ cannula	Oral/nasal airway	Endotracheal tube
Propofol	837	44	4	0	835	39	1
Chloral hydrate	30	3	0	0	10	0	0
Meperidine	15	0	0	0	6	0	0
Midazolam	78	4	0	0	38	0	0
Other G.A.	48	12	3	1	46	7	1
Other C.S.	25	1	0	0	10	0	0

Abbreviations: G.A. = general anesthetic; C.S. = conscious sedation.

Timing of procedures

There were 884 sedations in which G.A. was used and 149 in which C.S. was used. The time taken for different parts of the treatment process were analyzed in detail according to whether the patient received G.A. or C.S. Table 9 contains the details. The time from start of medication to "ready to treat" was much shorter with G.A., as these patients were normally sedated on the treatment table, whereas patients receiving C.S. were sedated in the recovery room and then transferred to the treatment room. However, there was a difference in the time taken to give radiation therapy treatment with each type of sedation. G.A. required a median of 8 min (75% complete within 12 min) vs. a median of 10 min (75% complete in 25 min) for C.S. When start of medication for sedation to the end of radiation treatment is measured, there is a median of 10 min (75% complete within 15 min) for G.A. vs. a median of 30 min (75% complete in 50 min) for C.S. The time from end of treatment to discharge was longer for G.A; a median of 52 min (75% complete in 61 min) vs. a median of 30 min (75% complete in 45 min) for C.S, reflecting the more intensive care taken before discharging patients who had received G.A.

Table 9. Timing of the treatment process (in minutes)

	General anesthetic (min)		Conscious sedation (min)	
Procedure	Median	75% complete	Median	75% complete
Start of medication to ready to treat	1	<2	10	<25
Ready to treat to start of treatment	0	<1	1	<5
Start of treatment to end of treatment	8	<12	10	<25
End of treatment to discharge	52	<61	30	<45
Start of medication to end of treatment	10	<15	30	<50
Start of medication to discharge	65	<74.5	61.5	<85

Statistical analysis

Univariate analysis. The following were not significant on univariate analysis. ECOG score, supine or prone position (including oxygen saturation), number of radiation fields used per treatment, males vs. females, and inpatients vs. outpatients.

Significant factors influencing the need for sedation included a mold of the head and neck only ($p = 0.007$), age ($p = 0.0001$), and the diagnosis of soft tissue sarcoma vs. lymphoma ($p = 0.008$).

Predicting a satisfactory treatment result were presedation status ($p = 0.0001$), and reliable i.v. access, with a portacath predicting a better result than a heplock ($p = 0.0001$). G.A. was more successful than C.S. ($p = 0.0001$) and the use of chloral hydrate in particular resulted in a less successful treatment outcome and a higher complication rate. C.S. results in a longer treatment time using expensive equipment than G.A. ($p = 0.0001$).

Multivariate Analysis

Table 10 shows the results of multivariate analysis using logistic regression. The only significant factor was that the odds of a more satisfactory treatment with a G.A. using propofol were 20 times those of a C.S. using either chloral hydrate, meperidine, or midazolam.

DISCUSSION

The sedation of children for radiation therapy has received sporadic attention in the medical literature, but a recent textbook of pediatric radiation therapy devotes a chapter to the subject (20). Recently (1999), a large retrospective series was reported from Duke University Medical Center on the use of anesthesia only for external-beam radiotherapy (EBRT) (21).

The variety of drugs used and the means of administering them reported in the literature gave no clear indication as to how sedation should be achieved for EBRT, which was the stimulus for this prospective study. In view of this uncertainty, it was accepted not to randomize the patients, but to start with a logical protocol, based on previous experience, which was almost entirely C.S. It was accepted that practice would change during the course of this study as experience developed.

Thirty-seven percent of our children required sedation vs.

Table 10. Multivariate analysis using logistic regression

Variable	Odds ratio	Variable	Odds ratio
Age	1.089	Supine/prone	1.613
Gender	1.248	Inpatient/outpatient	0.980
Performance status (P.S)	0.455	Diagnosis/leukemia	0.248
P.S.1	0.206	Diagnosis/CNS tumors	2.868
P.S.2	0.041	Propofol	20.615
P.S.3	0.233	Head and neck mould	2.598

24% from the Duke University Medical Center study (21). This high percentage may be related to the rigorous use of molds for immobilization (80% of all of our patients had molds and 96% of sedated patients), but problem with communication is probably the dominant reason; 50% of the radiation therapy staff are English-speaking expatriates, with a very limited knowledge of Arabic. The result was to develop information material for the patient and family during the course of this study; a video demonstrating the treatment process, a coloring book for the children explaining about cancer and its treatment with EBRT, and a book for older children and the family on the process; all in Arabic. Every child, whether selected for sedation or not, was introduced to the department and the machines by one of our Arabic-speaking nurses who spent time bonding with them. Even when this was not initially successful in avoiding sedation, it often resulted in the patient eventually accepting to try without sedation later in the course. During this study, an Arabic-speaking patient educator with a nursing background was appointed. Twenty percent of the patients who were selected for sedation on the basis of their anxiety did not subsequently require it. This could be attributed to the preparation process that the children went through.

Increasingly, there is evidence to support the logical theory that if children are given time and expert focused attention around their hospital experiences, their cooperation is more likely (22, 23). Trained play therapists are being increasingly employed in hospitals to help children understand, cooperate, and accept the difficult procedures they have to encounter during their treatment (24). This preparation through direct play helps obviate future psychologic problems that can occur due to their whole hospital experience. One of the authors (B.E.) was involved in developing a program at the University College London Hospital in the United Kingdom to prepare children with cancer for their radiation therapy treatment.

The program involved (*1*) clear instructions for parents/caregivers for each step in the process of the child's treatment; (*2*) guided picture storybooks that the family could borrow related to a child receiving radiation treatment; (*3*) a mock treatment machine (linear accelerator) with lights and buzzers situated in the playroom of the hospital for the child to use; (*4*) a large doll to enact treatments on and visualize their own fears; (*5*) time for familiarization with staff and equipment and many chances to interact with both; and (*6*) personalized star charts as a reward scheme for use each day the child attends for treatment.

All of these monitored games, incentives, and familiarization steps enabled the children to dispel some of their fears through transference. By making the process interactive, they could keep some control of the experience, and this enabled them to be more cooperative. This takes time and patience in a busy department, but the end result is that the number of children requiring C.S. or G.A. for their course of radiation therapy treatment can be reduced.

In patients receiving "curative" radiation therapy, once the optimum treatment position was decided upon, no concessions were made to the treatment plan to either avoid sedation, or to allow the continued use of C.S. rather than G.A., with the single exception of medulloblastoma, where, in borderline cases for sedation or where further convalescence was desirable, the patient might start with treatment of the posterior fossa in the supine position, rather than the craniospinal treatment in the prone position.

Our previous experience with C.S. led us to initiate therapy with chloral hydrate, meperidine, or midazolam. As a result of this study, we would not recommend chloral hydrate or meperidine for C.S.; meperidine because of its lack of effectiveness, and chloral hydrate because it lacks both effectiveness and safety. If C.S. is required, then i.v. midazolam appears to be the agent of choice. Its action is brief, reversible with flumazenil, and it has a reasonable margin of safety. However, it requires i.v. access, as its use by other routes (nasal or oral) is not yet confirmed as being a reliable method for EBRT sedation.

There are no prospective randomized studies that demonstrate the superiority of one anesthetic agent over another for EBRT. In this study, anesthetists had the discretion to use the agent of their choice for G.A., but were recommended to use propofol, which had been relatively untried in this hospital for children, and most did. As experience with this agent developed, it became the drug of choice, and, by the end of the study, most patients were simply being started immediately on a propofol G.A.

The choice of a satisfactory anesthetic for use outside the operating room has been discussed by Martin *et al.* (25) as (*1*) It must provide predictable, brief, anesthesia of adequate depth, and an immobile patient; (*2*) It must be able to be safely given repeatedly, with portable equipment; (*3*) A rapid awaking with short recovery time is desirable; (*4*) Maintenance of a patent airway in a variety of body positions and during transport is mandatory; (*5*) Provisions for standard monitoring is required for G.A. remote from the patient; and (*6*) Minimizing psychologic and physical trauma during the repeated procedures is desirable.

We found a propofol G.A. fulfilled all these criteria, particularly when given with a constant infusion pump. The rapid recovery and lack of sequelae meant that children were not hesitant to undergo the procedure, often proffering their i.v. line to the anesthetist in anticipation of their G.A. A major advantage is the maintenance of a patent airway in either a supine or prone position, such that intubation, either laryngeal mask or endotracheal, was not routinely required. Only 2 patients required endotracheal intubation during the study, and this included some seriously ill patients (26% had ECOG Status 3 or 4) as many patients in this developing country present with advanced cancer.

Although other agents are also recommended for their safety and efficacy, e.g., ketamine i.m. or i.v. (26), halothane or sevoflurane by inhalation (20), thiopental (9), or methohexital i.v. (27), we did not assess these. Intramuscular administration is not acceptable for repeated sedations. Defining the best anesthetic agent for EBRT would require a randomized clinical trial. Our G.A.'s with propofol were given safely by a variety of anesthetists. For either of our preferred agents, midazolam for C.S. and propofol for G.A., i.v. access is necessary. Without i.v. access, sedation is more problematic (93% satisfactory with i.v. access vs. 74% with no i.v. access available). Increasingly, for a prolonged radical course of radiation therapy under sedation, we are prepared to insert a portacath to ensure reliable i.v. access (16). With the frequent use of portacaths, there was no significant problem of pain on initial injection of propofol, which can be seen with peripheral i.v. access in a small vein.

Sixty-one of the 198 patients (32%) in this study had a central venous access. This reflects the increasing use of these devices in children in recent years for chemotherapy administration or for repetitive anesthesia or both. This emerging practice poses problems, as the device represents a potential source of contamination despite strict aseptic measures. This is particularly true for repeated use in immunocompromised and neutropenic patients. In our institution, during the period of this study, a total of 78 pediatric patients developed episodes of sepsis with positive blood cultures during chemotherapy and/or radiation treatment. In our study, 14 of 61 patients (23%) with venous access devices had sepsis, and, in 10 (16%), it had to be removed because of the sepsis and to document catheter infection. The incidence of sepsis in this study,however, is comparable to that reported in other studies (21, 28).

This hospital bulk funds its operations and does not yet itemize the cost of individual procedures. Thus, we were unable to compare the expense of C.S. with G.A. Nevertheless, there are undoubted efficiencies in using G.A. in reducing the time taken from start of sedation to the end of radiation therapy treatment (median, 10 min for G.A. vs. 30 min for C.S). This frees up both staff and expensive radiation therapy equipment. The certainty of a G.A. relieves the strain on nursing and medical staff who are using C.S. with all its uncertainty of whether the patient is sufficiently prepared for the procedure, and, particularly, relieving them of the decision on whether to supplement the dose if the patient is not prepared. The extra cost of having an anesthetist present has become less important, now that this hospital's latest guidelines for C.S. require the treating physician to be certified to give C.S. and to be present at all times during the C.S. procedure, which previously was delegated to appropriately certified nursing staff.

Weight loss after repeated sedation was not a significant problem.

The use of i.v. propofol has been associated in the past with contamination causing septicemia (29). This was traced to inappropriate preparation including lack of aseptic technique in handling the drug, and its prior preparation. The manufacturer recommends it as a single-use product that must be discarded within 6 h after initial use. It is a lipid-based anesthetic agent formulated in an emulsion of soybean oil, glycerol, and egg lecithin, and can support rapid microbial growth at room temperature. There is no evidence, however, that, by storing and using propofol strictly according to the manufacturer's instructions, there is any particular risk. In the United States, it is marketed with a preservative of disodium EDTA, but propofol used in the Middle East contains no preservative. In the retrospective survey from Duke University Medical Center (21), which covered the period from 1983 to 1996, they reported a 15% rate of sepsis using central venous lines. Six of the 11 episodes of central line sepsis in their series were in children repeatedly anesthetized with propofol, and they suggest that this agent increases the risk. In our series, 8 of 14 patients (57%) who developed sepsis during radiation treatment were repeatedly receiving a G.A. with propofol. These 8 patients, however, had other associated risk factors for infection. They had all received cytotoxic chemotherapy, and 5 developed treatment-induced neutropenia. All 8 patients had a portacath in place, 4 of which were infected. The incidence of sepsis in patients receiving a propofol G.A. was 13% (8/62). Careful monitoring of high-risk patients with portacaths receiving chemotherapy during their radiation therapy seems mandatory, while the suspicion that propofol increases the risk of sepsis persists (21, 28).

The manufacturer does not recommend the use of propofol in children under 3 years of age. The reasons for this are not entirely clear. In 1992, a memo was circulated from World Health Organization warning against the use of propofol for intensive care sedation in children (30). Its prolonged use in pediatric intensive care units had been associated with fatalities, in particular metabolic acidosis. However, no clear reason has been given to suggest a lack of safety and efficacy in young children for routine G.A.'s, and an editorial in 1995 suggested that this "probably reflects the lack of pediatric clinical trials rather than a proven clinical problem" (31). A survey of three teaching hospitals in New Zealand on attitudes toward the use of propofol for anesthesia in children under the age of 3 years revealed that 78 of 91 doctors who returned questionnaires were prepared to use propofol in these circumstances, and 62 admitted to using propofol in this age group in the previous 6 months (32). Kain *et al.* reported on a group of children receiving propofol for an MRI examination, The ages of the

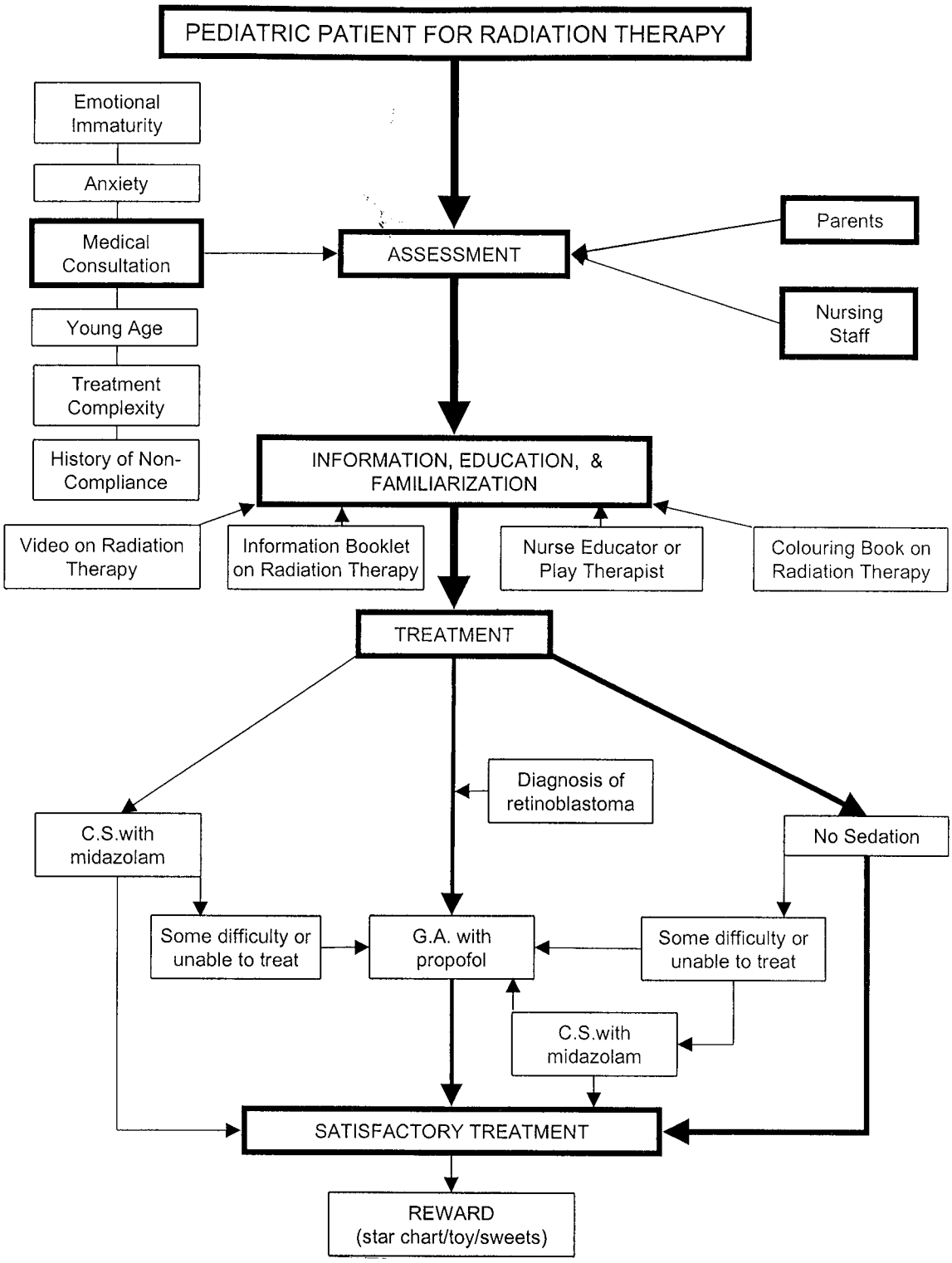

Fig. 2. Flow chart for sedation.

children ranged from 11 months to 6.5 years (33). Metriyakool states that continuous i.v. propofol is the standard anesthetic for children undergoing daily radiation therapy treatment at the Children's Hospital in Michigan and found it an acceptable drug in more than 500 treatments performed on 24 children aged 13 months–17 years, although aggressive behavior occurred in 2 patients while awakening from anesthesia (27). We have not seen this in our study. Scheiber *et al.* from Essen reported on 155 G.A.'s with propofol on 11 consecutive patients whose mean age was 30 months and "found it an excellent method to immobilize pediatric patients during radiotherapeutic procedures" (34).

In our study, 18 children under the age of 3 years (range, 0.75–2.9 years) received propofol without any significant problem. We already used it as our standard G.A. for retinoblastoma (16), where the median age of our patients was 31 months, because of its property of keeping the eye in the neutral position under a light anesthesia. Nearly all G.A. for radiation therapy requires a light anesthetic, not dissimilar to C.S., but more reliable and controllable. Finally, the diagnosis of a major illness, such as cancer, and its effective treatment, makes any theoretical risks more acceptable given the many qualities that propofol offers; in particular its rapid induction, its rapid and smooth emergence profile, its alleged antiemetic properties, and the apparent ability to maintain a patent airway when the head is rigidly fixed supine or prone in a mask, without the need for either laryngeal or endotracheal intubation.

Did departure from the protocol during the course of this study, by increasing the use of propofol G.A., without the prior use of C.S. bias these results? Given the poor results from C.S., it is unlikely that this would have affected the overall direction of the differences and would probably have magnified them further.

In this study, there were no serious complications of sedation in 1033 procedures. As a result of the study, we were able to develop tools for better preparation of the patient and family to try to reduce the need for sedation and reduce the indications for C.S., while confirming the efficacy and relative safety of a G.A. with propofol for EBRT. Figure 2 is a flowchart of the current process.

REFERENCES

1. Ries LAG, Hankey FR, Miller BA, *et al.*, editors. Cancer statistics review, 1973–1988. National Cancer Institute. NIH publication no.1991:91-2789. Bethesda, MD: NIH, 1991.
2. Jereb B, Krishnawami S, Reid A, *et al.* Radiation of medulloblastoma adjusted to prevent recurrence to the cribriform plate region. *Cancer* 1984;54:602–604.
3. Carrie C, Hoffstetter S, Gomaz F, *et al.* Impact of targeting deviation on outcome in medulloblastoma: Study of the French Society of Pediatric Oncology (SFOP). *Int J Radiat Oncol Biol Phys* 1999;45:435–439.
4. McCormick B, Ellsworth R, Abramson D, *et al.* Radiation therapy for retinoblastoma: Comparison of results with lens-sparing v. lateral beam techniques. *Int J Radiat Oncol Biol Phys* 1988;15:567–574.
5. Committee on Drugs of the Amican Academy of Pediatrics. Guidelines for the monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. *Pediatrics* 1992;89:1110–1115.
6. Bucholtz JD. Issues concerning the sedation of children for radiation therapy. *Oncol Nurs Forum* 1992;19:649–655.
7. Harrison GG, Bennet MB. Radiotherapy without tears. *Br J Anaesth* 1963;35:720–721.
8. Bennett JA, Bullimore JA. The use of ketamine hydrochloride anesthesia for radiotherapy in young children. *Br J Anaesth* 1973;45:197–201.
9. Menache L, Eifed PT, Kennamer DL, *et al.* Twice daily anesthesia in infants receiving hyperfractionated irradiation. *Int J Radiat Oncol Biol Phys* 1990;18:625–629.
10. Ferguson C, Kirkbride P. Anesthetic technique for radiotherapy in young children (Letter). *Int J Radiat Oncol Biol Phys* 1990;20:909.
11. Cassady JR, editor. Radiation therapy in pediatric oncology. New York: Springer-Verlag; 1994. p. 2–3.
12. Setlock MA, Palmasan BW. Propofol for radiation therapy in small children (Letter). *Anaesth Analg* 1992;75:860–861.
13. Aldridge LM, Gordon NH. Propofol infusions for radiotherapy. *Paediatr Anesth* 1992;2:133–137.
14. Casey WF, Paige V, Smith HS. Anesthesia and monitoring for pediatric radiotherapy. *J Roy Soc Med* 1986;79:454–459.
15. Brett CM, Wara WM, Hamilton WK. Anesthesia for infants during radiotherapy, an insufflation technique. *Anesthesiology* 1986;64:402–405.
16. Pradhan DG, Sandridge AL, Mullaney P, *et al.* Radiation therapy for retinoblastoma; A retrospective review of120 patients. *Int J Radiat Oncol Biol Phys* 1997;39(1):3–30.
17. Nicholson SC, Schreiner MS. Feed the babies. *Anesth Analg* 1994;79:407–409.
18. Cote CJ. Sedation protocols—Why so many variations? (Editorial). *Pediatrics* 1994;94:281–283.
19. Kupietzky A, Haupt MI. Pediatric midazolam: A review of its use for conscious sedation in children. *Pediatr Dentistry* 1993; 15(4):237–241.
20. Halperin PM, Constine LS, Tarbell NJ, *et al.*, editors. Pediatric radiation oncology. 3rd ed. Philadelphia: Lippincott—Williams & Wilkins, 1999. p. 563–575.
21. Fortney JT, Halperin EC, Hertz CM, *et al.* Anesthesia for pediatric external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 1999;44(3):587–591.
22. Slifer KJ, Bucholtz JD, Cataldo MD. Behavioral training of motion control in young children undergoing radiation treatment without sedation. *J Pediatr Oncol Nurs* 1994;11(2):55–63.
23. Pimm P, Fitzgerald E, Taylor L. Caring for children undergoing radiotherapy. *Radiography* 1997;3:27–30.
24. Pressdee D, May L, Eastman E, *et al.* The use of play therapy in the preparation of children undergoing MR imaging. *Clin Radiol* 1997;52(12):945–947.
25. Martin LD, Pasternak LR, Puddimat MA. Total intravenous anesthesia with Propofol in pediatric patients outside the operating room. *Anesth Analg* 1992;74:609–612.
26. Piwoz S, Goldstein B. The use of ketamine anesthesia in radiation therapy. *Radiology* 1973;109(3)725–726.
27. Metriyakool K. Methohexital as an alternative to propofol for intravenous anesthesia in children undergoing daily radiation treatments. A case report. *Anesthesiology* 1998;88:821–822.
28. Bow EJ, Kilpatrick MG, Clinch JJ. Totally implantable venous access ports systems for patients receiving chemotherapy for solid tissue malignancies, a randomized controlled clinical trial examining the safety, efficacy, costs, and impact on quality of life. *J Clin Oncol* 1999;17:1267–1273.
29. Nicholls RL, Smith JW. Bacterial contamination of an anesthetic agent (Editorial). *N Engl J Med* 1995;33:184–185.
30. World Health Organization. Warning against use of propofol (Diprivan®) for intensive care sedation in children. Alert no. 26. World Health Organization; 29 April 1992.
31. Meakin G. Role of propofol in paediatric anesthetic practice (Editorial). *Paediatr Anaesth* 1995;5:147–149.
32. Foy J, Nel P, Watts S. The use of propofol for anesthesia in children under the age of three years in New Zealand (Letter). *N Z Med J* 1998;111(1067):217.
33. Kain ZN, Gaal DJ, Kain TS, *et al.* A first pass cost analysis of propofol versus barbiturates for children undergoing magnetic resonance imaging. *Anesth Analg* 1994;79(6):1102–1106.
34. Scheiber G, Ribeiro FC, Karpienski H, *et al.* Deep sedation with propofol in preschool children undergoing radiation therapy. *Paediatr Anaesth* 1996;6:209–213.