REVIEW ARTICLE

The Management of Preoperative Anxiety in Children: An Update

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Anxiety in children undergoing surgery is characterized by subjective feelings of tension, apprehension, nervousness, and worry that may be expressed in various forms (1). Postoperative maladaptive behaviors, such as new onset enuresis, feeding difficulties, apathy and withdrawal, and sleep disturbances, may also result from anxiety before surgery. In fact, studies have indicated that up to 60% of all children undergoing surgery may present with negative behavioral changes at 2 wk postoperatively (1,2). Variables such as age, temperament, and anxiety of the child and parent in the preoperative holding area have been identified as predictors for these behavioral changes (1). Extreme anxiety during induction of anesthesia is also associated with an increase of these postoperative negative behavioral changes (3).

In addition to behavioral manifestations, preoperative anxiety activates the human stress response, leading to increased serum cortisol, epinephrine, and natural killer cell activity (4,5). This stress response can be activated by many different noxious stimuli including fear, anxiety, pain, cold, major surgery, and infection. The main components of the stress system are the corticotropin-releasing hormone and the locus ceruleus-norepinephrine/autonomic systems and their peripheral effectors, the hypothalamic pituitary-adrenal axis and the limbs of the autonomic system (5). There is also evidence for a bidirectional communication between the neuroendocrine system and the immune system. Stress activates the hypothalamic pituitary-adrenal axis, increases circulating glucocorticoids, and is associated with alterations of immune function and susceptibility to infection and neoplastic disease (6). The human response to surgical stress is characterized by a series of hormonal, immunological, and metabolic changes that together constitute the global surgical stress response (7,8). This perioperative response is considered a homeostatic mechanism for adapting to the perioperative injury. The effects of the surgical stress response, however, may be detrimental: neuroendocrine hormones (e.g., cortisol, catecholamines) and cytokines (e.g., interleukin-6) provoke a negative nitrogen balance and catabolism, delay wound healing, and cause postoperative immunosuppression (7,8). Children are particularly vulnerable to the global surgical stress response because of limited energy reserves, larger brain masses, and obligatory glucose requirements (9). Because acute psychological stress, such as preoperative anxiety, is associated with immediate stress hormone release, the contribution of perioperative psychological factors to the global perioperative stress response cannot be ignored. In adults, increased preoperative anxiety is associated with poor postoperative behavioral and clinical recovery (10,11).

As an indicator of the importance of preoperative anxiety, a panel of 72 anesthesiologists recently ranked various anesthesia low-morbidity clinical outcomes based on importance and frequency. The five clinical outcomes with the highest combined score were incisional pain, nausea, vomiting, preoperative anxiety, and discomfort from IV insertion (12). Thus, consensus is evident among anesthesiologists about the need to treat anxiety before surgery. In a modern epidemiological framework, diseases can be characterized in terms of risk factors, interventions, and outcomes. In this update, we will review preoperative anxiety in children using this conceptual framework (Fig. 1).

The Psychobiology of Separation

Learning to cope with separation from a parent is necessary for a child's normal development (13). Separation experiences such as going to school facilitate normal psychological development and personality organization. Other separation experiences, such as perioperative separation, may precipitate

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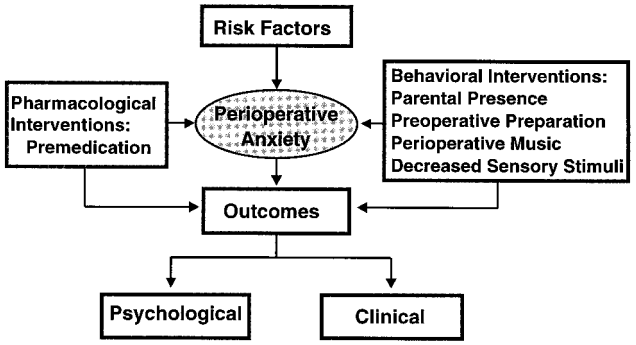

Figure 1. Conceptual framework of perioperative anxiety. Revised from (72).

confusion and anxiety. Between these two extremes, there are many separation experiences with varying degrees of psychobiological stress.

In the first weeks of life, infants are able to discriminate among people, but will accept care and comfort from adults other than their parents (14). By 3 mo of age, however, infants begin to respond differently to familiar and unfamiliar people. Older infants smile more at familiar people and may even try to engage their attention (14). Separation anxiety usually begins at 7–8 mo of age and peaks around 1 yr of age. In part, separation anxiety represents the infant's acquisition of new cognitive abilities and object permanence. The intensity of separation anxiety declines with age, largely because of increasing cognitive abilities and memory capacity. Frequently, however, the increase in abilities does not immunize toddlers and preschoolers against the stress and distress of separations.

The extent to which separation is traumatic or evokes adaptive responses reflects an individual child's developmental age, parenting experiences, genetic endowment, and environmental stability. For children with biologically based vulnerabilities, such as a sensitivity to novelty and transitions, even expected separations may impose a greater degree of stress than for less sensitive children (13). How parents help the child mediate a separation experience play a crucial role in the child's acute and long-term responses. In the extreme, the parent may be unable to mediate the experience for the child because of limitations such as severe anxiety. How well children have been cared for up to the time of the separation also influences their response to the stressor. Children deprived of attention in the home are at increased risk for stress in response to separations. Thus, the extent to which separations evoke adaptive responses reflects an individual child's genetics, personality, parenting, and previous life experiences.

Preoperative Anxiety: Identification

Identifying risk factors for development of preoperative anxiety is important, as more resources can be directed toward vulnerable children. Children 1–5 yr old are at the highest risk for developing extreme anxiety (1). This is not surprising considering the psychobiology of separation anxiety. Children who are shy or inhibited and those who have a high intelligence quotient and lack good adaptive abilities are also at increased risk (15). Previous surgery or hospitalization and poor response to visits to the pediatrician's office are also predictors for the development of preoperative anxiety. Finally, parental anxiety has been identified as a predictor for increased child's anxiety.

Preoperative Anxiety: Behavioral Modalities

Preoperative Preparation Programs

Most studies suggest that preoperative preparation programs reduce anxiety and enhance coping in children (16). These behavioral preparation programs have evolved significantly over recent decades. In the 1960s, preparation programs were designed to provide an orientation tour and narrative information and facilitate trust between the hospital staff, the child, and the parent (16). In the 1970s, modeling techniques were developed where children indirectly experienced the perioperative course by role rehearsal using dolls or by viewing a video (17). These modeling techniques were augmented in the late 1980s with child life preparation and the teaching of coping skills (17). Currently, development of coping skills is considered the most effective preoperative preparation intervention, followed by modeling, play therapy, operating room tour, and printed material (18). Although experts favor teaching of coping skills, most preparation programs in the United States consist of an orientation tour and printed information (18). Although coping preparation has been associated with reduction of anxiety in the preoperative holding area, no differences were found among the various preparation programs during induction, in the recovery room period, or postoperatively (19). Thus, the cost-effectiveness of child life specialists may or may not be justified by an associated reduction in preoperative anxiety.

Psychological preparation programs should be tailored to individual needs such as age, developmental stage, and previous experience (20). The priority of the age criterion relates to both the anxiety such exposure might generate and the length of time over which children can cope with anticipation. In addition, timing of the program before surgery is an important variable (20). Children aged ≥6 yr benefit most if they

participate in a preparation program ≥5 days before surgery and benefit least if the program is given only 1 day before surgery. This phenomenon is related to the way that children in this age group process new information. Finally, a child who has previously undergone surgery or has been hospitalized may develop an exaggerated emotional response to an information-based preparation program (20).

As increased parental anxiety results in increased child's anxiety (1), there is a need for interventions that are designed specifically for parents. Cassady et al. (21) demonstrated that parental preoperative anxiety decreased after viewing an educational videotape. We suggest that more parental interventions need to be developed and that a child's anxiety should be evaluated as an outcome.

Preoperative Anxiety: Behavioral Modalities

Parental Presence during Induction of Anesthesia. Parents and children prefer to stay together during medical procedures such as immunizations, dental treatment, and induction of anesthesia (22). Some data indicate, however, that parental presence during induction of anesthesia (PPIA) is allowed in 26% of US hospitals and is encouraged in only 8% of hospitals (23). In contrast, 28% of hospitals have no formal hospital policy and parental presence is against hospital policy for 32% of hospitals in the US. The smallest use of this induction technique was reported in the South-Central region and the highest in the Northwest and the Northeast (23). Interestingly, anesthesiologists from Great Britain (GB) encourage PPIA significantly more than anesthesiologists from the US (23,24). The reasons for these differences may include the use of different induction techniques, less concern about legal ramifications in GB, and a stronger demand for parental presence in GB. Economic issues such as operating room (OR) efficiency, infrastructure issues, lack of induction rooms and patchy preoperative educational programs, probably limit the availability of PPIA in the US.

Potential benefits from PPIA include reducing the need for preoperative sedatives and avoiding the fear and anxiety that may occur on separation to the OR. Other benefits, such as increasing the child's compliance during induction, remain controversial. Objections to PPIA include concern about disruption of the OR routine, crowded ORs, and a possible adverse reaction of parents. In addition, increased parental anxiety can increase a child's anxiety, prolong anesthetic induction, and place additional stress on the anesthesiologist.

Although early observational studies suggested reduced anxiety if parents were present during induction (25), more recent randomized controlled trials indicate that routine parental presence is not beneficial (26–28). One study demonstrated that only children >4 yr of age, those who have a "calm" baseline personality, or those who have a parent with a "calm" baseline personality benefit from this intervention (26). When interpreting the results of these studies, however, it should be noted that the design of a randomized controlled study does not reflect the practice of all anesthesiologists.

When data of survey studies are reviewed (23,24), it is noticed that most anesthesiologists use either PPIA or sedative premedication to treat preoperative anxiety. When sedative premedications were directly compared with PPIA, however, it was found that children receiving oral midazolam were significantly less anxious and more compliant during the induction process (27). A recent study examined whether a combination of PPIA and oral midazolam is more effective than oral midazolam alone (28). The investigators found that PPIA has no additive anxiolytic effects for children who received oral midazolam preoperatively. Parents who accompany their sedated children into the ORs, however, are significantly less anxious and more satisfied both with the separation process and with the overall anesthetic, nursing and surgical care provided (28).

PPIA is also associated with important legal implications. Lewyn (29) described a case in which a mother was invited to accompany her son into an emergency treatment room. According to the court, the mother fainted and suffered an injury to the head. In its verdict the Illinois Supreme Court stated that a hospital, which allows a nonpatient to accompany a patient during treatment, does not have a duty to protect the nonpatient from fainting. However, if medical personnel invite the nonpatient to participate in the treatment, then the hospital has a legal responsibility toward the nonpatient. Interestingly, some hospitals in the US now require the parents to sign a written informed consent acknowledging the risk of being present during induction of anesthesia.

We believe that future research interests should shift towards an emphasis on what parents actually do during induction of anesthesia, rather than simply on their presence. Allowing a parent into an OR without significant preparation may be counterproductive because some parent behaviors, such as criticism and commands, are associated with increased distress. Effective methods of training such as parental preparation programs can be developed for enhancing the effects of PPIA.

Preoperative Anxiety: Pharmacological Modalities

The reported rate of use of pharmacological modalities for the treatment of preoperative anxiety in the US varies widely among age groups and geographical locations (24). Premedicant sedative drugs are least

often used with children <3 yr of age and most often used with adults <65 yr of age (25% vs 75%). Currently, the most commonly used sedative premedicant in the preoperative holding area is midazolam (85%), followed by ketamine (4%), transmucosal fentanyl (3%), and meperidine (2%) (Fig. 2). The majority of children in the US are premedicated via the oral route (80%), followed by the intranasal route (8%), the IM route (6%), and the rectal route (3%).

Midazolam. Midazolam is a short-acting benzodiazepine that is very lipophilic at physiologic pH, which accounts for its rapid onset of action. Davis et al. (30) has demonstrated that intranasally administered midazolam in a dosage of 0.2–0.3 mg/kg in patients undergoing myringotomies led to satisfactory separation from parents and a satisfactory induction over 70% of the time and did not prolong recovery time and hospital discharge time. Midazolam administered intranasally is effective in reducing anxiety in children within 10–12 min (31). A major drawback of intranasally administered midazolam, however, is that at least 50% of children cry on administration because it transiently irritates the nasal passages. Midazolam can also be given as a nasal spray, which is effective in reducing procedural anxiety in children undergoing cancer therapy (32). Midazolam can be administrated sublingually at the same dosage as intranasally. Although sublingual administration of midazolam is associated with a decreased incidence of crying (18%), it may be difficult to prevent small children from either swallowing the midazolam or spitting it out immediately (33).

Rectal administration of midazolam in doses of 0.5–1.0 mg/kg effectively reduces the anxiety of children before induction of anesthesia (34). Although the incidence of hiccups after IV midazolam is <2%, the incidence noted that in a recent study involving rectally administered midazolam was more than 20% (34). The investigators had no explanation as to the increased rate of hiccups other than the young age of the children, but they found that the hiccups were easily treated by ethyl chloride nasal spray (34).

Orally administered midazolam (0.5 mg/kg) has been shown to significantly reduce preoperative anxiety in young children (27,28). Orally administered midazolam can be given in a dosage of 0.25 mg to 1.0 mg/kg up to total dose of 20 mg depending on the duration of surgery and the anxiety level of the child. A commercially available and Food and Drug Administration-approved midazolam in a syrup form of 2 mg/mL became available in 1998. Suresh et al. (35) examined different doses of the commercially available midazolam and found that 0.25 mg/kg resulted in satisfactory sedation and anxiolysis in a majority of patients within 20 min. This study also found that increasing the dose resulted in an increase in the proportion of patients with satisfactory sedation and a shortened time to onset of action (35). Other authors report that the minimum time interval for successfully separating premedicated children from their parents is 10 min with a peak sedative effect occurring between 20 and 30 min (36).

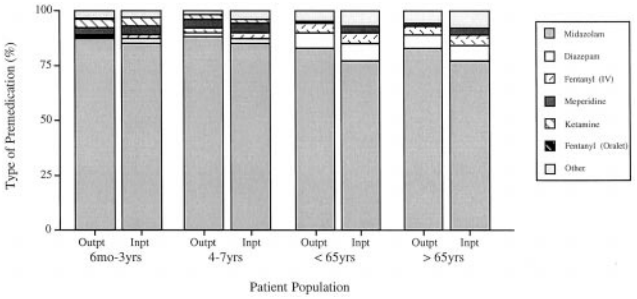

Figure 2. Types of premedicants used in the preoperative holding area (23).

The issue of orally administered midazolam and delays in the discharge of patients is controversial. Although several recent studies noted that orally administrated midazolam is not associated with a delayed discharge (28,29,37), two studies involving children undergoing adenoidectomy report that emergence and recovery are delayed in the children who receive oral midazolam preoperatively (38,39). Another study involving children who underwent myringotomies using sevoflurane or halothane anesthesia indicated that children who were given oral midazolam experienced significant delays in recovery time but no delays in discharge time from the hospital (40). Finally, Martlew et al. (41) have addressed the issue of a combination of preoperative oral midazolam and propofol-based anesthetic. The investigators found that propofol infusion requirements decrease by one-third and discharge readiness was delayed in children who had been given midazolam preoperatively. The investigators suggested that the increased postoperative sedation may have been attributable to synergism of propofol and midazolam on GABA receptors (42).

As indicated above, a significant proportion of children experiences maladaptive behavioral changes after outpatient surgery (1). In one investigation, children who were premedicated with oral midazolam had a significantly decreased incidence of negative behavioral changes during the first week after surgery (43). However, this study noted that by 2 wk postoperatively there were no significant differences between the midazolam and placebo groups. The mechanism by which midazolam decreases the incidence of postoperative behavioral changes is not clear but it may be related to amnesia of the perioperative process (44). Children who received a benzodiazepine for dental extractions and were amnestic about the experience tolerated further dental treatments better than children who were not amnestic about their initial dental

Table 1. Premedications Administered by the Oral Route

Premedication (reference)	Dose (mg/kg)	Bioavailability	Time of Onset (min)	Time of Peak Action (min)	Elimination half-life T1/2 (hr)
Midazolam (36,37,69)	0.25–1.0	27–36%	10	20–30	2
Clonidine (62)	0.002–0.004	>90%[a]	45	60–90	8–12
Ketamine (53,55)	3.0–6.0	16%[b]	10	20–30	2–3

[a] In adults; [b] Active metabolite norketamine is twice as high in oral form.

Table 2. Premedications Administered Transmucosally and Rectally

Medications (reference)	Dose mg/kg	Bioavailability	Time of Onset (min)	Elimination Half-life (t ½ hrs)
Midazolam (intranasal) (30,32)	0.2–0.3	83%	<10	2–3
Midazolam (rectal) (35,40,70)	0.3–1.0	50%	10	2–3
Oral Transmucosal Citrate (49–52)	0.01–0.015	33%	30	7
Ketamine (intranasal) (71)	3–5	50%	<10	3
Ketamine (rectal) (71)	5–6	25%	20–30	3

extractions (45). This finding may be particularly important for children undergoing repeated surgical procedures. Memory becomes impaired in children after oral midazolam as early as 10 min and anxiolytic effects are apparent as early as 15 min after administration (44). This short timing to onset of amnesia is of particular importance in busy surgery centers where the turnover of cases is very quick.

Midazolam and diazepam can be reversed with flumazenil, which antagonizes benzodiazepines competitively. The initial recommended dose in children is 0.05 mg/kg given IV in a titrated fashion of up to 1.0 mg total. Some children who are reversed with flumazenil will experience resedation, so it is prudent to monitor them for 1–2 h (46). Adequate drug levels can also be reached intranasally in a dose of 40 μg/kg given by drops from a syringe (47).

Fentanyl. Fentanyl is a synthetic opioid that is very lipophilic, which makes the drug a good candidate for administration across mucosal and dermal barriers. Oral transmucosal fentanyl citrate (OTFC) administered in the form of a lozenge attached to a stick and known as the OTFC was the first sedative drug approved by the Food and Drug Administration in 1993 for use in children. Oral transmucosal citrate in 200-, 300-, and 400-μg dosage units is mixed in a raspberry-flavored candy matrix and given to children in the dosage of 10–15 μg/kg for absorption transmucosally. Its sedative effect is often associated with facial pruritus, which usually occurs 30–45 min after children begin to consume the lozenge.

OTFC sedates children before induction of anesthesia (48–51). OTFC does not, however, reliably lead to decreased apprehension or improved cooperation with induction in young children (48–51). In a small percentage of patients, OTFC can cause a respiratory depression leading to clinically significant oxygen desaturation, so a clinician skilled in airway management must be present while this drug is administered (48). OTFC usage in children is associated with a frequent incidence of postoperative nausea and vomiting that is not easily antagonized by prophylactic droperidol (49). In fact, at least one study was prematurely terminated because of a very frequent incidence of preoperative vomiting (48). A significant advantage of OTFC is that it decreases the postoperative narcotic requirement (50). Dsida et al. (50) reported that preoperative OTFC is as effective as IV fentanyl (2 μg/kg) given intraoperatively for management of postoperative analgesia in children undergoing tonsillectomy.

Ketamine. Ketamine is an arylcycloalkylamine that produces a state of sedation, immobility, analgesia, amnesia, and dissociation from the environment. An advantage of ketamine compared with other premedicants is that it causes less respiratory depression when given in equipotent sedative doses (52). A disadvantage of ketamine as compared with other premedicants is the association of increased salivary and bronchial secretions, which can lead to laryngospasm (53). Ketamine can also cause muscle rigidity and nystagmus in children, which can alarm parents if they are not informed about this characteristic. An increased incidence of postoperative emesis is associated with preoperative administration of ketamine (54, 55). The above side effects are all dose related and can be diminished with the use of a small dose of orally administered ketamine (3 mg/kg) (54). Unfortunately, the time of onset of the action of orally administered ketamine is also dose related with large-dose orally administered ketamine (6 mg/kg) having an onset of action of 10 min and small-dose ketamine leading to sedation within 20 min (54,55).

Ketamine administration may be associated with agitation and hallucinations during the postoperative period (55,56). Two recent studies have found that concurrent use of a benzodiazepine given to children undergoing ketamine sedation did not affect the incidence of postprocedure agitation (55,56). In addition, the incidence of postoperative nightmares, restless sleep, and nocturia is no different in children receiving ketamine, midazolam, or a combination of ketamine and midazolam together (55).

The IV preparation of ketamine can be mixed with cola or fruit syrup to create an oral mixture of ketamine, which is favorably accepted by most children. Ketamine can be also be given intranasally (3–5 mg/kg), transmucosally (5–6 mg/kg), rectally (5 mg/kg), and IM (2–5 mg/kg) (57,58).

Postanesthesia care unit discharge time of children who received orally administered ketamine is reported not to be prolonged compared with orally administered midazolam provided that duration of surgery is longer than 30 min (55). Ketamine administered IM in an emergency room setting, however, was found to significantly delay discharge and increase costs compared with midazolam administered rectally or intranasally (59).

Funk et al. (55) reported that the combination of midazolam and ketamine administrated orally had a 90% success rate of satisfactory anxiolysis compared with <75% with either drug alone. An oral ketamine/midazolam mixture was also found to be superior to IM meperidine, promethazine, and chlorpromazine in children undergoing pediatric cardiac catheterization (60). The ketamine/midazolam mixture provided superior sedation and amnesia and there was less need for IV propofol rescue as compared with the IM regimen (60).

Clonidine. Clonidine is an α2 adrenergic agonist first developed as an antihypertensive agent but later found to have analgesic, anxiolytic, and sedative properties (61). Orally administrated clonidine in a dose of 4 μg/kg reliably causes sedation, decreases anesthetic requirements, and decreases requirement for postoperative analgesics (61–63). End-tidal halothane requirements decrease by almost 50% in children premedicated preoperatively with clonidine (62). This decrease in minimum alveolar concentration requirement may be secondary to the analgesic effect of clonidine as well as a primary hemodynamic effect (62). Preoperatively administered clonidine is also as effective as intraoperatively administered fentanyl (3 μg/kg) for postoperative analgesia in children undergoing tonsillectomies (64). The recovery profile of children who receive clonidine is similar to the recovery profile of children who receive oral diazepam (0.2 mg/kg), but clonidine causes significantly less postoperative psychomotor impairments as compared with diazepam (65,66).

One major drawback for the use of clonidine as a sedative premedicant is its slow onset of action. Clonidine has to be administered orally as early as 45 min before surgery (61). In children, peak plasma concentration is at 60–90 min for orally administered clonidine and 50 min for rectally administered clonidine (61).

New Directions for the Future

Future research efforts should concentrate on the development of sedatives that will be well tolerated, have a very short time for onset of anxiolysis, and have short duration of action. In addition, newly developed preoperative sedatives should possess properties such as antegrade amnesia and should ideally decrease intraoperative anesthetic requirements and reduce postoperative analgesic requirements. Finally, new methods of delivering sedative premedications should also be developed. For example, transdermal applications of medications should be investigated as well as oral transmucosal delivery methods for medications other than fentanyl. Simple transdermal medications usually take at least 1 h for minimally effective serum concentrations of drugs to be reached unless iontophoresis is used. Iontophoresis can significantly speed the transfer of medication across a dermal surface and has been effective in delivering fentanyl in adults within 10 min at 2 mA (67). Finally, the effectiveness of alternative treatment modalities such as acupuncture should be investigated (68). Further research is needed in these areas.

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