

A Survey of Pain Management and Procedural Sedation Practices by Pediatric Hematology/Oncology Practitioners in China

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ABSTRACT

Background: The provision of supportive care is increasingly a priority of quality care in pediatric oncology settings. In China, the quality of supportive care services may vary among regions because of differences in social and health indicators.

Objectives: To evaluate Chinese pediatric oncology practitioners' pain management practices, and identify barriers to optimal pain control in children with cancer undergoing invasive procedures in China.

Methods: Oncology practitioners were recruited from pediatric cancer centers and professional groups in Hong Kong and mainland China through convenience sampling. Respondents completed a paper-based or electronic structured questionnaire. Chi-square test was conducted to compare practitioners' responses across geographical regions of their practices.

Results: The sample (n=304) consisted of pediatric oncologist/hematologists (n=149, 49%) and allied health professional (n=155, 51%), who practiced in the South China region (n=189, 62%) and North China/other regions (n=115, 38%). As compared to practitioners from the South China region, practitioners from the North/other regions were less likely to administer procedural sedation during lumbar puncture (78% vs 48%; $P<0.0001$) and bone marrow aspiration (72% vs 46%; $P=0.0012$). Regardless of region, practitioners identified the lack of formal training (72%) and dedicated staff (77%), and restricted access to sedative drugs (70%), as major barriers to adopting procedural sedation. Physicians who practiced in South China were more likely than those in North China/other regions to report the use of opioids for moderate-to-severe pain, such as morphine (70% vs 49%; $P=0.013$) which is the recommended first-line strong opioid for persistent pain in children. Practitioners indicated parents' concerns with opioid addiction (73%), safety (76%) and stigma (63%). Practitioners also reported inadequate knowledge in dosing opioids (48%) and side effects management (48%). Overall, 37% of practitioners perceived that even with existing measures, children still experienced severe pain (pain score of 5-10) during procedures.

Conclusion: Our results suggest the relative inadequacy of procedural control in certain regions of China. We

have identified potential institutional barriers and gaps in physicians' knowledge and education about the use of procedural sedation and strong analgesics. There is an urging need to empower oncology practitioners and review policies to facilitate implementation of procedural sedation for children in China.

Keywords

Cancer, Children, Suboptimal pain management, Oncology.

Introduction

Children with cancer are repeatedly exposed to treatment-related pain and invasive medical procedures [1-3]. According to many studies, treatment-related and procedural pain are often the worst causes of pain experienced by children with cancer [3]. Suboptimal pain management can lead to acute physiological responses such as tachycardia and perspiration, psychological distress and a fear of needles [1,4], which may have adverse effects on the child's quality of life from diagnosis until long-term survivorship. Therefore, procedural pain treatment is now considered an integral part of care for a cancer patient, especially in the context of pediatric procedures such as bone marrow aspiration (BMA), lumbar puncture (LP), peripherally inserted central catheter (PICC) insertion and endoscopic procedures [2,5].

The literature describes multiple cultural, language and neurodevelopmental factors contributing to poor pain management in children with cancer [1,2,5]. Children may receive suboptimal pain treatment because of difficulties in the perception and articulation of painful sensations [6,7]. Therefore, it is important to use appropriate pain assessment tools to avoid underestimating the child's complaints and enable an accurate evaluation of his/her pain symptoms and intensity. Unfortunately, oncology practitioners have a limited understanding of pain assessment tools, and the available methods for identifying pediatric pain often fail to recognize the associated symptoms [5,6,8].

Many international organizations now recommend the use of procedural sedation, which is broadly defined as the administration of sedatives or dissociative agents (with or without analgesics) to induce a state that will allow the child to tolerate unpleasant painful procedures while maintaining cardio-respiratory function [5,9-11]. However, the administration of procedural sedation is often complex and demanding of resources and training. Strong opioids and benzodiazepines, the most commonly used sedation agents, can increase a patient's risk of drug-related adverse events such as hemodynamic and respiratory instability, prolonged mechanical ventilation, withdrawal symptoms, delirium and hallucination [12]. Despite mounting evidence supporting the use of procedural sedation, oncology practitioners may not be adequately trained to provide proper sedation care [13].

China encompasses a broad geographic area with a diversity of cultures and traditions. Cultural factors may influence beliefs, behavior, perceptions and emotions related to pain, all of which have important implications for healthcare practices [6]. In a recent qualitative study, 11 Chinese pediatric hemato-oncologists from an academic hospital in a remote city of Northwest China related their

anecdotal experiences and revealed that poor pain management was largely due to a lack of awareness about the long-term effects of uncontrolled pain in children, inadequate knowledge of the use of analgesia and sedation and a lack of anesthesiology support regarding general analgesia [13]. Few data are available on pain management and procedural sedation practices in pediatric oncology units across China. Although China is a unified country, the quality of supportive care services may vary among regions because of differences in social and health indicators. Increasingly, emphasis is placed on the delivery of cost-effective and optimal clinical care on curative intent. Therefore, it is important to determine the procedural sedation practices used in hospitals across China and thus identify the barriers to implementing quality pain services, as well as strategies to overcome these limitations.

Advances in risk stratification and risk-based treatment strategies have led to a gradual improvement in childhood cancer survival rates in China [14]. Accordingly, the provision of supportive care is increasingly a priority of quality care in pediatric oncology settings. This study was designed to evaluate the perceptions of pediatric oncology practitioners regarding the pain experienced by children with cancer in association with invasive diagnostic/therapeutic procedures. The overarching aim of this study was to unite clinicians and policymakers throughout China in achieving the shared goal of delivering effective pain management practices in children with cancer. We also examined the current pain management practices of pediatric oncology practitioners across China and identified barriers to the use of procedural sedation and/or strong analgesics.

Methods

This multicenter, cross-sectional survey was conducted between April and October 2019. Prior to study initiation, approval was obtained from the Survey and Behavioral Research Ethics Committee of the Chinese University of Hong Kong and from the Institutional Review Board of the Guangzhou Women and Children's Medical Center in Guangzhou, China.

Respondents

A convenience sampling approach was used to recruit oncology practitioners from major pediatric oncology and hematology centers and through key professional study groups in mainland China and Hong Kong. Respondents considered eligible for this survey met the following criteria: (1) status as a practicing physician, nurse or pharmacist; (2) current practice in a pediatric cancer center or pediatric oncology department of a medical institution located in Hong Kong or mainland China; and (3) current provision of clinical care to and interactions with pediatric cancer patients for at least 50% of the work shift. These criteria enabled us to target a homogenous sample of practitioners who were involved directly in the management of cancer patients.

Questionnaire Design

We designed a questionnaire based on the existing literature to assess the pain management practices applied to children with cancer, with a specific focus on the use of strong analgesics and procedural sedation (Table 1). The questionnaire, which began with a short paragraph describing the overall objective of the study, comprised five sections. The first section collected information about the respondents' demographic details and clinical experiences, including age, sex, profession, rank and specialization, as well as the region, setting and years of healthcare practice. The second section comprised four questions designed to gather information about the respondents' general pain management practices, methods of pain assessment, common drugs used to manage moderate to severe pain in children and perceived barriers to the use of opioids in children. The third section concerned the practitioners' assessment of pain control associated with seven types of medical procedures: LP, BMA, bone marrow biopsy, PICC insertion, venipuncture, intramuscular injection and subcutaneous injection.

Practitioners were asked to rate the perceived degree of pain (on a scale of 0–10) experienced by children during each of the above medical procedures both without pharmacological intervention and after the administration of pain control measures. The fourth section began with a definition of procedural sedation (Table 2) [9-11], and the practitioners were asked to indicate whether they applied procedural sedation for LP, BMA, bone marrow biopsy and PICC insertion. The respondents were also asked about the level of sedation (minimal, moderate or deep sedation or general anesthesia) and the pharmacological agents used for each of these medical procedures. Furthermore, the respondents were asked to identify challenges associated with administering procedural sedation from a list of common practitioner-related and institutional barriers. The last section concerned the practitioners' practices and the perceived effectiveness of non-pharmacological comfort measures for pain management.

The survey was initially formulated in English and was translated

Table 1

Objectives	Questions	Options
To evaluate practitioners' method of pain assessment in children [1,2,3]	Briefly describe how pain assessment in children is conducted in your practice.	<ul style="list-style-type: none"> No pain assessment conducted Parents/caregivers are asked to proxy-rate the child's level of pain Physician or Nurse routinely observes for signs of pain Child is asked: Regarding the absence or presence of pain To indicate their pain on a scale To provide a pain score Others:
To evaluate practitioners' general management of pain in children with cancer [1,2,3]	Select the best option that describes your current practice of pain management in children.	<ul style="list-style-type: none"> The WHO Two-step Analgesic Ladder Guidelines Other international guidelines Local hospital guidelines Adopt senior colleagues' practices Clinical judgment Others
	Indicate the analgesics that you most commonly prescribe, or you most commonly observe in your practice, to manage moderate to severe pain in children.*	<ul style="list-style-type: none"> Paracetamol NSAID Morphine Fentanyl Hydromorphone Oxycodone Tramadol Propofol Others
To identify practitioner-related, institutional and parent-related barriers to the use of opioids in children [1]	<p>Indicate your level of agreement with the following statements concerning the use of opioids in children</p> <p>Practitioner-related misconceptions/ concerns: Opioids should be avoided in children. Increasing analgesic requirements is a sign that the child is becoming addicted. Early use of the opioids reduces its future efficacy. Opioids should only be reserved in terminal stages of cancer. I feel inadequate in dosing opioids in children. I feel inadequate in managing the side effects of opioids in children.</p> <p>Parent-related concerns: Parents are concerned about opioid addiction. Parents are concerned about the adverse effects of opioids. Parents are concerned about the stigma associated with opioid use.</p> <p>Institutional barriers: The regulation of opioids in my institution is too restrictive. I am concerned about regulatory scrutiny.</p>	<ul style="list-style-type: none"> Strongly agree Agree Neutral Disagree Strongly disagree Not sure

<p>To evaluate practitioners' perceived effectiveness of current pain control measures [1,2,3]</p>	<p>Using a scale of 0 (no pain) to 10 (worse pain), indicate your perceived degree of pain on children: When the procedures are conducted without pharmacological intervention When the procedures are conducted under your routine pain control practices</p>	<ul style="list-style-type: none"> • Lumbar puncture • Bone marrow aspirate • Bone marrow biopsy • PICC catheter insertion • Venipuncture • Intramuscular injection • Subcutaneous injection
<p>To evaluate practitioners' procedural sedation practices in children with cancer [1]*</p>	<p>Indicate with the level of sedation you subject the child to during: Lumbar puncture Bone marrow aspirate Bone marrow biopsy PICC insertion</p> <p>Indicate drug(s) that you most commonly prescribe for procedural sedation during: Lumbar puncture Bone marrow aspirate Bone marrow biopsy Insertion of peripherally inserted central catheter</p>	<ul style="list-style-type: none"> • No procedural sedation used • Minimal sedation • Moderate sedation • Deep sedation • General anesthesia • No procedural sedation used • Anxiolytic agents (diazepam, lorazepam) • Opioids (morphine, fentanyl, hydromorphone) • Short-acting benzodiazepines for sedation (midazolam) • α-2 agonist (clonidine, dexmedetomidine) • Anesthetic (ketamine, esketamine) • Propofol • Diphenhydramine • Others
<p>To identify practitioner-related, institutional and parent-related barriers to the use of procedural sedation in children [1]</p>	<p>Regardless of whether you practice procedural sedation, indicate with the relevance of the following challenges you face concerning the use of procedural sedation for painful procedures in your institution:</p> <p>Institutional barriers: Lack of space (hospital beds, recovery areas) Lack of equipment and logistics (airway management equipment, intravenous equipment, emergency medications) Lack of dedicated staff for managing sedation-analgesia Sedative drugs are not available in the hospital formulary Sedative drugs are available in the formulary but restrictions are applied for their use in painful procedures by non-anesthetists doctors</p> <p>Practitioner-related misconceptions/ concerns: Inadequate training in administering the sedation procedure (eg. Unsure of the appropriate dose and monitoring parameters) Lack of adequate training in managing the adverse effects associated with sedation (eg. cardio-pulmonary resuscitation course for cardiovascular collapse) Healthcare providers are generally unsure of the current guidelines in pain management Healthcare providers are concerned about the safety and long-term adverse effects of sedation Healthcare providers do not perceive the need for sedation-analgesia Healthcare providers are fearful of potential litigation or liability issues</p> <p>Parent-related concerns: Parents have concerns about cost Parents have concerns about safety</p>	<ul style="list-style-type: none"> • Very relevant • Somewhat relevant • Not relevant
<p>To identify practitioners' practice and perceived effectiveness of non-pharmacological interventions for procedural pain</p>	<p>Indicate if your institution adopts non-pharmacological comfort measures for pain management (yes or no), and your perceived effectiveness (effective, neutral, or not effective) of these methods in controlling pain.</p>	<ul style="list-style-type: none"> • Pre-procedural pain counselling to child • Pre-procedural pain counselling to parent • Distraction (play, videos) • Relaxation techniques (massage) • Hypnosis • Breathing exercises • Music • Heat and /or cold compresses • Applying pressure or vibration
<p>¹Differences in responses were evaluated between respondents from different geographical regions: South China versus North China/China/another region. ²Differences in responses were evaluated between respondents of different professional roles: physicians versus allied healthcare provider (non-physicians). ³Differences in responses were evaluated between respondents with different length of clinical experience: Less than 10 years of clinical experience versus respondents with more than 10 years of experience. *Analyses for these questions were only performed among respondents who identified themselves as "physicians" as physicians typically make key prescribing decisions in most clinical settings within China.</p>		

Table 2

	Patient conscious	Responds to repeated or painful stimuli	Airway	Spontaneous ventilation	Cardiovascular function	Common drugs/ combination of drugs
Minimal	Conscious	Yes	Unaffected	Unaffected	Unaffected	• Benzodiazepine
Moderate	Depressed consciousness	Yes, respond to verbal tactile stimuli	Unaffected	Unaffected	Unaffected	• Benzodiazepine +/- opioid (eg: Fentanyl)
Deep	Depressed consciousness and cannot be easily aroused	Yes, respond to repeated or painful stimuli	May require intervention	May be inadequate	Usually maintained	• Short-acting sedative agents (eg: Propofol, etomidate, or a benzodiazepine) • Propofol +/- ketamine
General anesthesia	Loses consciousness	No	Often require intervention	Usually inadequate	Impaired	• Barbiturates • Opioid

American Academy of Pediatrics, American Academy of Pediatric Dentistry, Cote CJ, Wilson S, Work Group on Sedation. Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures: An Update. *Pediatrics* 2006;118:2587.

Godwin SA, Burton JH, Gerardo CJ, Hatten BW, Mace SE, Silvers SM et al. Clinical Policy: Procedural Sedation and Analgesia in the Emergency Department. *Annals of Emergency Medicine* 2014;63:258.e18.

Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018: A Report by the American Society of Anesthesiologists Task Force on Moderate Procedural Sedation and Analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. *Anesthesiology* 2018;128:437-79.

Sheta SA. Procedural sedation analgesia. *Saudi Journal of Anaesthesia*. 2010;4(1):11-16.

into Simplified Chinese by two independent bilingual investigators. Differences in the official language used in different regions of China led practitioners from Hong Kong to complete the English version on paper, while practitioners in mainland China adopted an electronic version disseminated through “WeChat”, the most widely and frequently used social media platform among Chinese people. WeChat was also listed among the most common platforms used by Chinese physicians to acquire medical knowledge in a mobile environment [15]. Self-administration of this questionnaire required approximately 15–20 minutes.

Statistical analysis

Descriptive statistics were used to evaluate the oncology practitioners’ responses to each question. The analyses of procedural sedation practice and the choices of sedatives and strong analgesics included only physicians, as these professionals often make key prescribing decisions in most Chinese clinical settings. Allied healthcare providers typically play a supportive role in pain assessment and management. The chi-square test was used for secondary analyses in which the categorical responses were compared between the following predefined groups: (1) physicians (pediatric oncologists and hematologists) and allied healthcare providers (nurses, pharmacists etc.), (2) practitioners with more or fewer than 10 years of clinical experience in pediatric oncology/hematology and (3) groups defined by the geographical locations of their healthcare practices. All analyses were conducted using SAS (SAS 9.4, SAS Institute, Cary NC).

Results

Sample characteristics

A total of 304 respondents, including physicians (49%), nurses (42%) and pharmacists (9%), completed the questionnaire (Table 3). The majority of respondents practiced in the South China region (62%) and at either public hospitals (47%) or academic medical institutions (51%). Approximately half of the practitioners (47%) possessed more than 10 years of healthcare experience, and the most frequent specialties were pediatric oncology (74%) and hematology (66%).

	Frequency	n	(%)
Age (years)	20 – 29	81	(26.6)
	30 – 39	118	(38.8)
	40 – 49	66	(21.7)
	50 – 59	34	(11.2)
	Above 60	5	(1.6)
Sex	Male	238	(78.3)
	Female	66	(21.7)
Profession	Physician	149	(49.0)
	Junior level	21	(14.1)
	Mid-level	43	(28.9)
	Senior	85	(57.1)
	Nurse	129	(42.4)
Primary area(s) of practice*	Pharmacist	26	(8.6)
	Pediatric oncology	225	(74.0)
	Pediatric hematology	199	(65.5)
	Pediatric surgery	17	(5.6)
Years of clinical experience in pediatric oncology or/and hematology	General pediatrics	45	(14.8)
	Less than 1 year	23	(7.6)
	1 – 4	68	(22.4)
	5 – 9	65	(21.4)
	10 – 14	41	(13.5)
	15 years and more	103	(33.9)
Region of practice#	Missing	4	(1.3)
	South China region	189	(62.2)
Primary practice setting	North China and other regions	115	(37.8)
	Community/ government/ municipal / provincial hospital	142	(46.7)
	Academic/ university/ research centers	155	(51.0)
	Private practice	7	(2.3)

Table 3: Demographic Information and Clinical Experience of Respondents (n=304).

*Numbers do not add up as practitioners may have multiple areas of primary practice.

South China region (“Hua-nan”) refers to the Hong Kong Special Administrative Region, and cities in the Guangdong, Guangxi and Hainan provinces. They are grouped together as these provinces have similar socioeconomic indices, cultural background and healthcare practices.

Pain assessment and overall pain management practices

Overall, the majority of respondents had adopted either international (46%) or local hospital (26%) recommendations to guide their clinical decision-making (Table 4). Differences in practices were observed between regions. A higher proportion of respondents from South China had adopted the recommendations of local institutional guidelines and in-house pain teams, compared with those from North China or other regions (33% vs 16%; $P=0.0005$). Respondents with fewer than 10 years of practice were more likely to rely on the clinical experiences and supervision of their senior colleagues, compared to more experienced respondents (17.3% vs 7.6%; $P=0.0009$).

The most common pain assessment approaches involved behavioral observation by a healthcare provider during the procedure (72%) and the child’s report of the presence of pain (71%) (Table 4). Compared with physicians, allied healthcare providers were more likely to use validated pain scales (44% vs 69%; $P<0.0001$) and pain scores (47% vs 72%; $P<0.0001$) in their practices. Respondents from the South China region were also more likely than respondents from other regions to conduct formal pain assessments using validated pain scales ($P=0.0018$). In the absence of pain control interventions, the majority of respondents perceived LP (70%), BM aspiration (78%), BM biopsy (91%)

and PICC insertion (69%) as procedures that inherently induce moderate (pain score of 5–7) or severe pain (pain score of 8–10) in children (Figure 1). Even after applying currently available pain control measures, 32–37% of respondents still perceived that their pediatric patients experienced moderate to severe pain during these painful procedures, indicating the inadequate effectiveness of these measures (Figure 1).

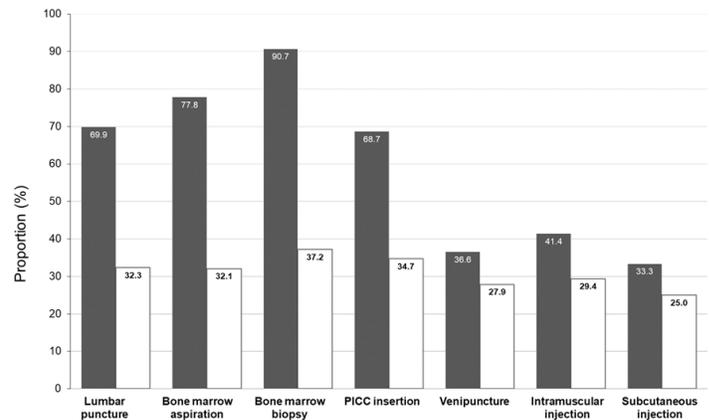


Figure 1: Perceived Pain and Effectiveness of Pain Control Associated with Common Medical Procedures in Children with Cancer (n=304).

Grey bars: Proportion who perceived moderate (pain score 5 to 7) to severe pain (pain score 8 to 10) associated with each procedure without any pain control measures.

White bars: Proportion who perceived moderate (pain score 5 to 7) to severe pain (pain score 8 to 10) associated with each procedure, after current pain control measures are applied.

	All (n=304)	Analysis Stratified by Profession		p	Analysis Stratified by Region		p	Analysis Stratified by Clinical Experience		P	
		Physicians (n=149)	Allied healthcare providers (n=155)		South China (n=189)	North China/ others (n=115)		< 10 years (n=156)	≥ 10 years (n=144)		
Best description of pain management practices#	n (%)	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)		
WHO Two-step Analgesic Ladder Guidelines and other international guidelines	139 (45.7)	71 (47.7)	68 (43.9)	<0.0001	86 (45.5)	53 (46.1)		72 (46.2)	66 (45.8)	0.0009	
Local guidelines from hospital or/and pain team	80 (26.3)	18 (12.1)	62 (40.0)		62 (32.8)	18 (15.7)		44 (28.2)	34 (23.6)		
Adopting senior colleagues’ practices	47 (15.5)	23 (15.4)	15 (9.7)		22 (11.6)	16 (13.9)		27 (17.3)	11 (7.6)		
Solely based on clinical judgement	38 (12.5)	37 (24.8)	10 (6.4)		19 (10.1)	28 (24.3)		13 (8.3)	33 (22.9)		
Pain assessment method*	n %	n %	n %	p	n %	n %	p	n %	n %	P	
No pain assessment conducted	12 (4.0)	5 (3.4)	7 (4.5)	0.60	8 (4.2)	4 (3.5)	0.74	4 (2.6)	5 (3.5)	0.64	
Observation by physician or nurses	219 (72.0)	107 (71.8)	112 (72.3)	0.93	145 (76.2)	74 (64.3)	0.020	108 (69.2)	108 (75.0)	0.26	
Child is asked:	Regarding the presence of pain	217 (71.4)	105 (70.5)	112 (72.3)		138 (73.0)	79 (68.7)	0.42	115 (73.7)	100 (69.4)	0.41
	To indicate their pain on a scale (Visual analogue scale, Faces Pain scale)	172 (56.6)	65 (43.6)	107 (69.0)	0.73	120 (63.5)	52 (45.2)	0.0018	92 (59.0)	78 (54.2)	0.40
	To provide a pain score (eg. pain score)	182 (59.9)	70 (47.0)	112 (72.3)	<0.0001	126 (66.7)	56 (48.7)	0.0019	99 (63.5)	81 (56.3)	0.20

Table 4: Pain Management Practices in Children with Cancer (n=304).

Respondents were asked to select only one response that best describes his/her practice. Comparison was conducted among predefined groups (profession, region and years of clinical practice) for the overall adopted practice.

*Respondents could select more than one response. Comparison was conducted among predefined groups (profession, region and years of clinical practice) for each pain assessment method.

Level of Sedation	Lumbar puncture				Bone marrow aspiration				Bone marrow biopsy				PICC Insertion			
	South China (n=60)		North China and others (n=89)		South China (n=60)		North China and others (n=89)		South China (n=60)		North China and others (n=89)		South China (n=60)		North China and others (n=89)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
No Sedation	10	(16.7)	44	(49.4)	15	(25.0)	46	(51.7)	11	(18.3)	34	(38.2)	17	(28.3)	36	(40.5)
Any sedation	47	(78.3)	43	(48.3)	43	(71.7)	41	(46.0)	46	(76.6)	49	(55.0)	42	(70.0)	49	(55.0)
Minimal/moderate sedation	35	(58.3)	35	(39.3)	30	(50.0)	35	(39.3)	32	(53.3)	40	(44.9)	30	(50.0)	35	(39.3)
Deep	12	(20.0)	8	(9.0)	13	(21.7)	6	(6.7)	14	(23.3)	9	(10.1)	12	(20.0)	14	(15.7)
General anesthesia	3	(5.0)	2	(2.3)	2	(3.3)	2	(2.3)	3	(5.0)	6	(6.7)	1	(1.7)	4	(4.5)
<i>P</i>	<0.0001				0.0012				0.0096				0.13			

Table 8: Physicians' Practices for Painful Procedures in Children with Cancer (n=149).

PICC: Peripherally inserted central catheter.

Analysis was only performed among respondents who identified themselves as "physicians" as physicians typically make key prescribing decisions in most clinical settings within China.

Comparison was conducted between proportion of physicians who adopted sedation and those who did not adopt sedation at all, across the 2 pre-defined geographical regions for each specific procedure.

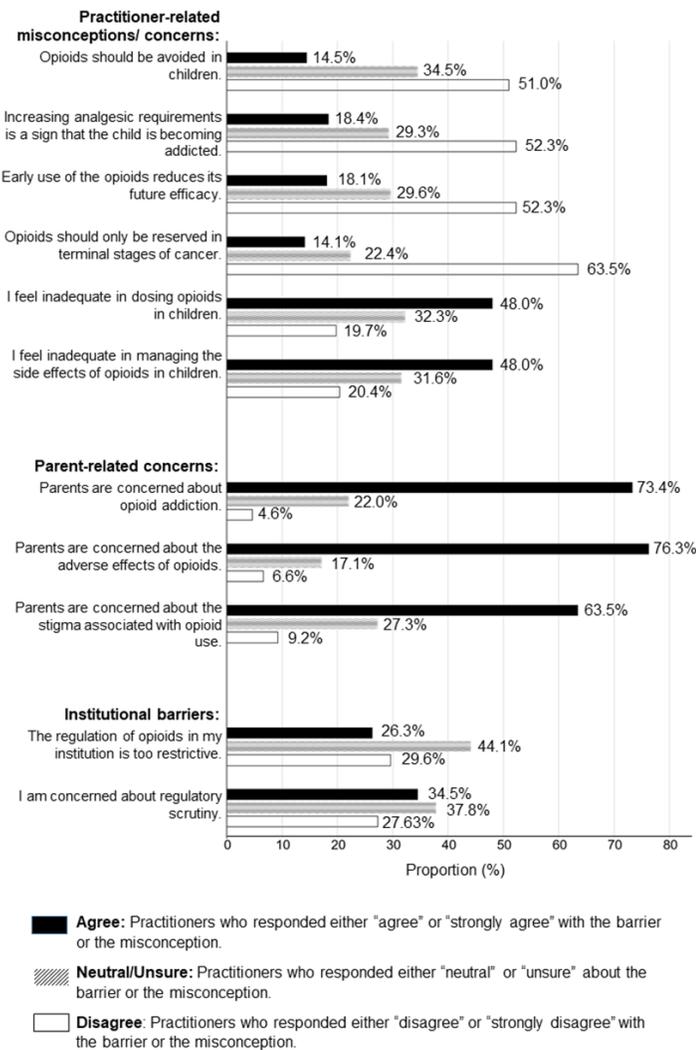


Figure 2: Barriers to the Use of Opioids in Children with Cancer (n=304).

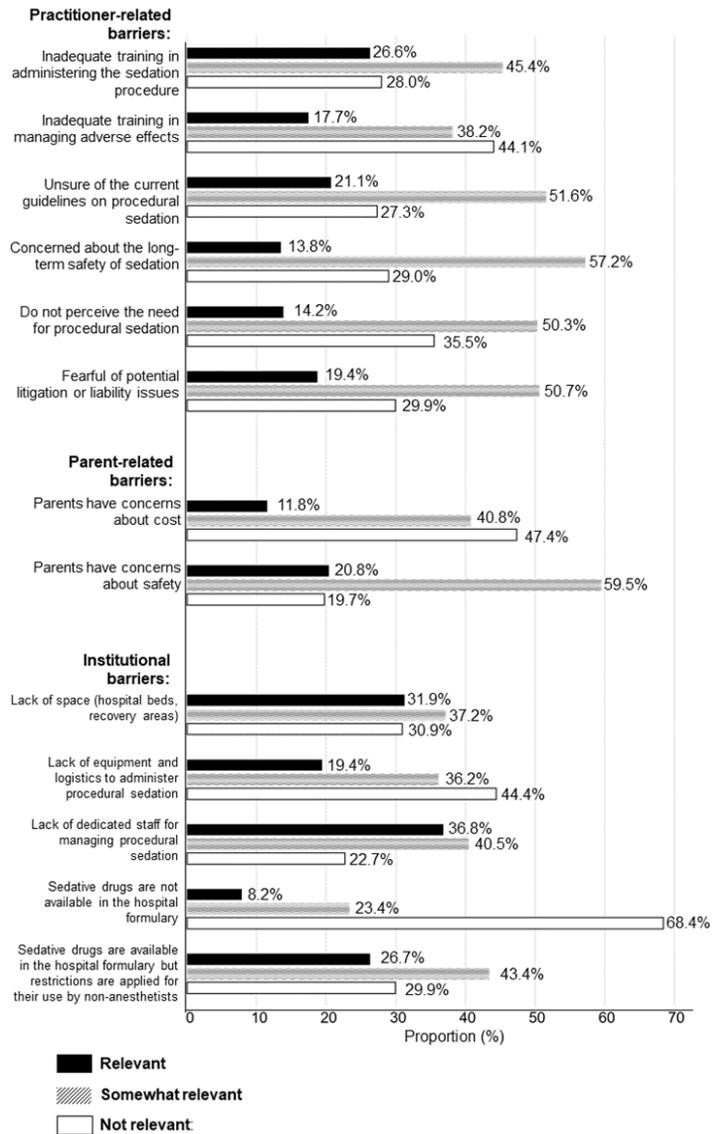


Figure 3: Barriers to the Use of Procedural Sedation in Children with Cancer (n=304).

No statistically significant differences in the perceived effectiveness of current practices were observed between respondents from different regions or with different levels of clinical experience (Table 5). However, allied healthcare providers were more likely to report inadequate pain management during LP, compared to physicians (21% vs 11%; $P=0.028$). Similar trends were also observed for other procedures, although those differences were not statistically significant (Table 5).

Physicians ($n=149$, Table 6) who participated in the study were asked to identify the analgesics that they would prescribe to children experiencing moderate to severe pain. Overall, non-steroidal inflammatory drugs (NSAID) (79%), tramadol (69%) and fentanyl (61%) were the most commonly prescribed analgesics (Supplement 5). Differences in the physicians' prescribing patterns were observed between geographical regions. Physicians who practiced in the South China region were more likely than those in North China and other regions to report the use of opioids, such as morphine (70% vs 49%; $P=0.013$), fentanyl (75% vs 52%; $P=0.00042$) and tramadol (78% vs 63%; $P=0.05$) (Table 7).

Use of opioids for moderate to severe pain

Half of the respondents identified inadequate training in the dosing, monitoring and management of side effects as a barrier to the use of opioids in children with cancer (Figure 2). Interestingly, 14-18% of the respondents harbored misconceptions, including the avoidance of opioids in children (15%) and reservation of opioids only for patients in the terminal stages of cancer (14%), as well as the misinterpretation of signs of opioid tolerance as opioid addiction (18%). Respondents also reported the restrictive nature of the opioid formulary in their institutions (26%), as well as concerns about regulatory scrutiny (35%). Three quarters of the respondents also identified parents' concerns about addiction, adverse effects and stigma as major barriers to the use of opioids in their pediatric patients. Respondents from North China and other regions were more likely to report inadequate opioid administration and management than respondents from the South China region (Figure 4).

Use of procedural sedation

Stark differences in procedural sedation practices were observed between regions (Table 8). Procedural sedation was more commonly administered for painful procedures in children with

cancer by physicians in the South China region, compared to those in North China and other regions ($P<0.05$ for all). Up to half of the physicians from North China performed LP (49%) and BM aspiration (52%) without procedural sedation, compared with 17% and 25% in South China, respectively.

In the overall cohort, the respondents commonly cited a lack of confidence in administration (72%), lack of awareness of current guidelines (73%) and fear of potential litigation or liability issues (70%) as practitioner-related barriers (Figure 3) to conducting procedural sedation. Respondents also identified institutional barriers such as inadequate space (69%) and facilities (56%), a lack of dedicated staff (77%) and a restrictive sedative formulary for non-anesthetists (70%). Compared with respondents from South China, a larger proportion of respondents from North China and other regions identified inadequate training, inexperience with guidelines and parental concerns regarding costs as major barriers (Figure 5).

Use of non-pharmacological pain control measures

Distraction methods (59%) and the provision of pre-procedural pain counselling to the parent (51%) and child (49%) were the most frequently practiced non-pharmacological pain control measures (Table 9). Other measures reported less frequently included relaxation techniques, breathing exercises and music.

Method	Used in clinical practice	
	n	(%)
Pre-procedural pain counselling to parent	154	(50.7)
Pre-procedural pain counselling to child	149	(49.0)
Distraction (play, videos)	178	(58.6)
Relaxation techniques (massage)	111	(36.5)
Hypnosis	42	(13.8)
Breathing exercises	87	(28.6)
Music	101	(33.2)
Heat and /or cold compresses	60	(19.7)
Applying pressure or vibration	25	(8.2)
Others*	9	(3.0)

Table 9: Use of Non-pharmacological Interventions in Children with Cancer ($n=304$).

Table 5

		Lumbar puncture#		Bone marrow aspiration#		Bone marrow Biopsy#		PICC Insertion#	
		n	%	n	%	n	%	n	%
Regions	South China ($n=189$)	29	(15.8)	29	(15.8)	34	(18.5)	31	(17.1)
	North China/ Others ($n=115$)	18	(16.4)	21	(19.3)	22	(20.2)	20	(18.2)
	P-value	0.89	0.44	0.72	0.82				
Professionals	Physicians ($n=149$)	16	(11.2)	20	(14.0)	23	(16.1)	20	(14.2)
	Allied healthcare provider ($n=155$)	31	(20.5)	30	(20.0)	33	(22.0)	31	(20.7)
	P-value	0.028	0.17	0.19	0.14				
Years of clinical experience	< 10 years ($n=156$)	21	(13.6)	21	(13.6)	23	(14.9)	22	(14.3)
	≥ 10 years ($n=144$)	25	(18.4)	28	(20.7)	32	(23.7)	29	(21.8)
	P-value	0.26	0.10	0.05	0.09				

Table 5: Difference Perceived Effectiveness of Pain Control Associated with Common Medical Procedures in Children with Cancer.

#Proportion who indicated severe pain (pain score 7 to 10) after pain control measures are applied.

Demographics		Physicians (n=149)		Non-physicians (n=155)	
		n	%	n	%
Age (years)	20 – 29	15	(10.1)	66	(42.6)
	30 – 39	59	(39.6)	59	(38.1)
	40 – 49	41	(27.5)	25	(16.1)
	50 – 59	29	(19.5)	5	(3.2)
	Above 60	5	(3.4)	0	(0)
Sex	Male	60	(40.3)	6	(3.9)
	Female	89	(59.7)	149	(96.1)
Profession	Physician	-	-	-	-
	Junior level	21	(14.1)	-	-
	Mid-level	43	(28.8)	-	-
	Senior	85	(57.1)	-	-
	Nurse	-	-	129	(83.2)
Primary area(s) of practice*	Pediatric oncology	112	(75.2)	113	(72.9)
	Pediatric hematology	119	(79.9)	80	(51.6)
	Pediatric surgery	4	(2.7)	13	(8.4)
	General pediatrics/ other pediatric specialties	6	(4.0)	39	(25.2)
Years of clinical experience in pediatric oncology or/and hematology	Less than 1 year	10	(6.8)	13	(8.4)
	1 – 4	20	(13.4)	48	(31.0)
	5 – 9	30	(20.1)	35	(22.6)
	10 – 14	21	(14.1)	20	(12.9)
	15 years and more	68	(45.6)	35	(22.6)
	Missing	0	(0)	4	(2.6)
Region of practice#	South China region	60	(40.3)	129	(83.2)
	North China and other regions	89	(59.7)	26	(16.8)
Primary practice setting	Community/ government/ municipal/ provincial hospital	50	(33.6)	92	(59.4)
	Academic/ university/ research centers	95	(63.8)	60	(38.7)
	Private practice	4	(2.7)	3	(1.9)

Table 6: Demographic Information and Clinical Experience of Respondents Stratified by Profession.

*Numbers do not add up as practitioners may have multiple areas of primary practice.

South China region (“Huanan Qu”) refers to the Hong Kong Special Administrative Region, and cities in the Guangdong, Guangxi and Hainan provinces. They are grouped together as these cities have similar socioeconomic indices and cultural background.

Pharmacological interventions		All Physicians (n=149)		South China Region (n=60)		North China and others (n=89)		P
		n	%	n	%	n	%	
Strong analgesics	NSAID	117	(78.5)	43	(71.7)	74	(83.1)	0.09
	Tramadol	103	(69.1)	47	(78.3)	56	(62.9)	0.046
	Fentanyl	91	(61.1)	45	(75.0)	46	(51.7)	0.0042
	Morphine	86	(57.7)	42	(70.0)	44	(49.4)	0.013
	Paracetamol	62	(41.6)	35	(58.3)	27	(30.3)	0.0007
	Oxycodone	27	(18.1)	20	(33.3)	7	(7.9)	<0.0001
	Hydromorphone	17	(11.6)	10	(16.7)	7	(7.9)	0.082
Sedatives	Short-acting benzodiazepines	58	(38.9)	28	(46.7)	30	(33.7)	0.11
	Anxiolytic agents	48	(32.2)	21	(35.0)	27	(30.3)	0.55
	Anesthetic	29	(19.5)	19	(31.7)	10	(11.2)	0.0020
	α-2 agonist	17	(11.4)	1	(1.7)	16	(18.0)	0.0021
	Propofol	18	(12.1)	9	(15.0)	9	(10.1)	0.37
	Opioids	16	(10.7)	10	(16.7)	6	(6.74)	0.055

Table 7: Physicians’ Top Strong Analgesics and Sedative Agents across Regions (n=149).

Analysis was only performed among respondents who identified themselves as “physicians” as physicians typically make key prescribing decisions in most clinical settings within China.

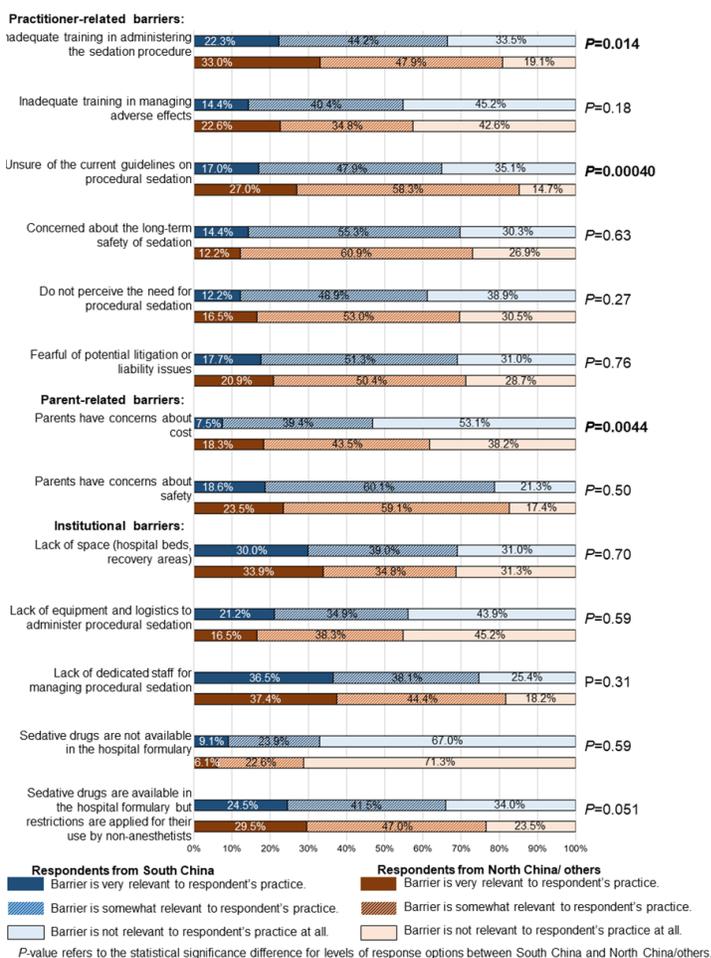
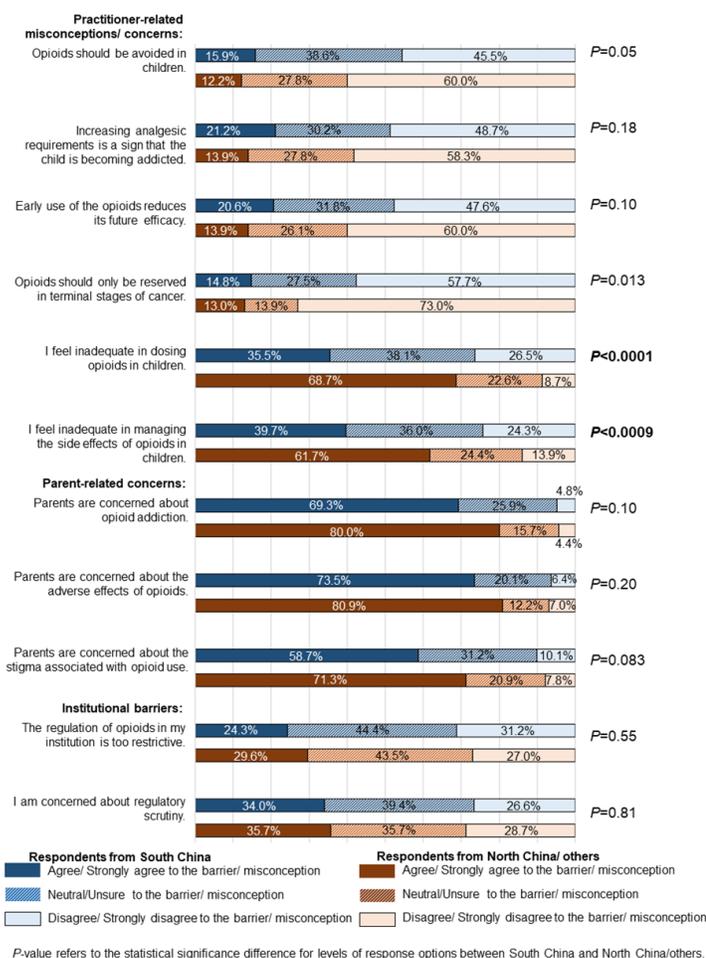


Figure 4: Differences between South China (Blue) and North China/others (Brown) in Barriers towards the Use of Strong Analgesics (n=304).

Figure 5: Differences between South China (Blue) and North China/others (Brown) in Barriers towards the Use of Procedural Sedation (n=304).

Discussion

To the best of our knowledge, this was one of the largest studies to evaluate the practices and perspectives of Chinese pediatric oncology practitioners regarding the administration of painful procedures to children. Additionally, this was the first study to compare practices among different geographical regions within China and identify areas requiring improvements in pain management. The oncology practitioners reported varied practices and levels of consensus regarding procedural sedation and the choice of first-line analgesics for children with moderate to severe pain. Regardless of region, however, oncology practitioners recounted that Chinese parents expressed fear and stigma regarding the use of strong analgesics, as well as safety concerns about sedatives. The practitioners also highlighted an inadequate level of knowledge and skill regarding the administration of procedural sedation and dosing of opioids, as well as institutional barriers that restricted their access to sedatives.

Although mainland China has experienced progressive advances in cancer support and palliative care [16], the topic of pain management in pediatric oncology remained as an under-researched and under-addressed area. Improvements are needed,

as up to 37% of our respondents perceived the inadequacy of current pain control measures applied to children undergoing painful procedures. In particular, our study identified poor pain management education as a major concern, as reflected by the fair proportion of respondents who indicated concerns regarding the use of opioids and the answers to questions requiring knowledge about pain assessment and drug use. Our results were consistent with those of a qualitative study by Wang et al., which revealed that Chinese pediatricians had insufficient knowledge about analgesia and sedation usage due to a lack of formal pain management education for healthcare providers [13]. This issue is exacerbated by the lack of specific Chinese reference standards regarding pediatric procedural pain management. These results support the development of continual professional education programs to improve the knowledge and skills of all oncology practitioners regarding the provision of pain control. The proper administration of procedural sedation includes a pre-sedation assessment of the suitability of the patient for sedation, selection of an appropriate agent based on knowledge about the pharmacology of sedatives, continuous monitoring of patients and an emergency resuscitation protocol to address potential airway or circulatory complications [5,10,11]. Such formalized programs should target the education of

both senior and junior practitioners regarding the characterization and psychological burden of pain, pain assessment skills and the practical and theoretical knowledge about pain management and the pharmacology of analgesics and sedatives.

Physicians and allied health professionals gave slightly different responses concerning the perceived effectiveness of current pain control measures for medical procedures in children with cancer. Compared to physicians, a higher proportion of allied healthcare providers reported the inadequate management of current pain control measures during LP procedures. Specifically, a higher proportion of allied healthcare providers reported the use of pain scores and pain scales to assess procedural pain in children, whereas physicians seemed to rely more on clinical observations. Similar differences in the pain assessments of healthcare professionals have been reported in the literature [7,8]. One study reported that physicians tend to underestimate pediatric pain, as reflected by a low concordance between the child's and physician's perceptions of pain [8]. This discrepancy may be partly attributable to an unawareness or underestimation of anxiety and traumatic stress, which could exacerbate the child's perception of pain. These collective findings highlight the importance of a multimodal strategy involving the observation of pain-related behavioral and psychological changes in the child and the application of a formal pain assessment using well-established pain rating scales. Such intentional approaches are necessary. In particular, the Chinese population is known to be culturally less expressive when verbalizing pain and parental perceptions, as well as being less aware of the psychological effects of uncontrolled pain in children and harboring misconception that procedural pain is inevitable and necessary for effective treatment [13,17].

The World Health Organization recommends a 2-step approach to general pain management [18]. A 2-step analgesic ladder includes relatively cost-effective medicines, such as NSAIDs and morphine, in a stepwise approach. Paracetamol and ibuprofen are recognized as first-line options for mild pain, whereas opioids are recommended as the second step for the treatment of moderate to severe pain. Specifically, many international guidelines recommend morphine as a first-line strong opioid for the treatment of persistent moderate to severe pain in children with medical illnesses [18]. However, only 57% of all physicians in our study reported the use of morphine in their patients. Therefore, the physicians in our sample might have been reluctant to treat pain with opioids due to inadequate knowledge about the dosing regimen and parents' fears about addiction and adverse effects. Practitioners in the South China region seemed less likely to prescribe NSAIDs as a first-line option for moderate to severe pain, compared to practitioners from other regions in China. This discrepancy may be attributed to pain guidelines issued in Hong Kong and the southern cities of mainland China, which discourage the use of NSAIDs in children with cancer due to concerns about thrombocytopenia. Regionally, a structured educational program that encourages the increased use of strong opioids is needed, and robust evidence demonstrates that such programs can improve pain remission rates, especially in patients with moderate to severe pain [19-21]. An education model

is also needed to correct the misconceptions held by patients and parents, overcome their aversions to strong opioids and empower them with essential information about the safe dosing, storage and disposal of opioids.

Currently, procedural sedation is recommended for children during painful procedures [5,9,12]. Although the majority of respondents indicated that they provided some degree of sedation to their pediatric patients, the clinical approaches differed across geographical areas. To the best of our knowledge, few current regional guidelines in mainland China dictate the methodology of procedural sedation and indicate the most effective interventions. The reasons underlying the observed discrepancies are likely multifactorial and may include differences in the culture, education or training backgrounds of healthcare professionals and the available resources. In the absence of a dedicated team, institutional limitations, including space (e.g., hospital beds, recovery areas) and equipment support (e.g., airway management equipment, intravenous equipment, emergency medications), may pose challenges to the administration of procedural sedation. Pediatric cancer centers in Hong Kong generally allow pediatricians to administer procedural sedation. In contrast, pediatricians at some institutions in mainland China may prefer to perform these procedures under general anesthesia provided by a trained anesthesiologist [13,22]. However, hospitals in mainland China are often burdened by high patient volume with each anesthesiologist delivering sedation care for up to 50 patients per day in some rural hospitals [22], while sedation training provided to non-anesthesiologists is often inadequate. Such hectic environment and demanding workload create a significant barrier for pediatric oncology teams to adopt procedural sedation. In our study, oncology practitioners from certain regions of South and North China also indicated a restricted access to and/or availability of opioids and sedatives due to regulatory obstacles and a lack of health policies advocating such pain services. Therefore, hospital administrators and policymakers must support and direct sustainable changes in each unique institutional setting.

Older children and adolescents may choose to undergo certain procedures without sedation, given the deleterious adverse effects associated with sedatives and strong analgesics. In such cases, healthcare providers should adopt alternatives to reduce the child's anxiety in the absence of sedation. Emerging evidence now supports the use of non-pharmacological comfort measures for both adult and pediatric patients [1,23,24]. Our results demonstrated that comfort measures, such as distraction, music and pre-procedural counselling, are commonly used in clinical settings, despite limitations on robust efficacy or guidelines regarding implementation in the pediatric cancer population. These measures may be popular because of the ease of use and relatively low cost. Specifically, various advantages of a novel approach involving virtual reality as an interactive form of distraction include the requirement for less-specialized facilities and the provision of an immersive environment that distracts the child's attention from the painful environment [25]. In Hong Kong, an ongoing research study is evaluating the use of immersive virtual reality

interventions for pain and anxiety in pediatric cancer patients. The preliminary results suggest positive outcomes, namely the reduction of psychological distress in children [26]. Future studies should aim to evaluate the efficacy profiles and efficacies of non-pharmacological interventions for reducing the intensity of sedation or strong analgesia during painful pediatric procedures.

We hope that the findings from this study will encourage the pediatric oncology community in China to establish a nationwide breakthrough pain and procedural pain management program for children with cancer. In 2011, the Ministry of Health of the People's Republic of China launched the Good Pain Management (GPM) program, which aimed to standardize the treatment of cancer pain, improve the quality of life of patients with cancer and promote quality cancer-related health care services [27]. GPM originated from the "Professional Committee of Cancer Rehabilitation and Palliative Care of the Guangdong Anti-cancer Association" in South China [28]; this may explain our findings that higher proportion of practitioners in South China who endorsed systematic pain management protocols in their practices, as compared to respondents from other regions of China. By early 2016, 67 national wards and 769 provincial wards were accredited, and an increasing number of hospitals in mainland China have implemented and adhered to a common set of guidelines for the establishment of GPM wards. This group recently published promising short-term outcomes observed after raising the standard of care for pain management in cancer wards, as reflected by significant increases in the consumption of strong opioid drugs and pain-related health literacy in Chinese patients [27]. However, the GPM in China mainly targets adult oncology patients. Therefore, procedural pain management for pediatric cancer patients is not adequately addressed. Limited evidence is available to support the treatment of cancer breakthrough pain and procedural pain in children. Further research-driven practices and clinical consensus from experts are needed to encourage good pain management, specifically in children with cancer. Based on the findings of this study, systematic and evidence-based pain management facilities and protocols are needed for children with cancer who experience cancer pain and/or are undergoing invasive procedures at accredited childhood cancer treatment hospitals throughout China. These efforts will enable the eager promotion and provision of effective pain management for children with cancer throughout China.

Limitations

The findings of this study should be considered in the context of several limitations. This study used a convenience sampling method that did not allow us to calculate response rates to support the representability of our findings. Although this survey was disseminated to different pediatric oncology study groups in China, more than half of the surveyed oncology practitioners practiced in South China. Hence, the external validity of the study findings should be interpreted cautiously. Because the electronic version of the survey was distributed through social media and returned anonymously, it was not possible to determine the validity of every entry. However, efforts were made to disseminate the survey through professional pediatric oncology workgroups and

major pediatric oncology institutions in China. This approach may have helped to establish the sampling frame and likely reduced the risk of recruiting ineligible or careless respondents. Despite the limitations associated with the online survey, this approach has been widely accepted as an effective means of collecting behavioral data from individuals in a large geographical region. We emphasize that this study should be interpreted as an effort to understand the perceptions and practices of the medical community in China and to generate future directions for addressing gaps in research and knowledge. However, the findings from this study should not be considered the primary and sole evidence on any aspect of this subject matter.

Conclusion

This study solicited the perspectives of a reasonably large sample of pediatric oncology/hematology specialists across China regarding the various aspects of pain management practices. Our results suggest the relative inadequacy of procedural control in certain regions of mainland China. We have identified potential institutional barriers and gaps in physicians' knowledge and education about the use of procedural sedation and strong analgesics. These findings provide critical information to support service planning, policy making and capacity building activities intended to overcome these gaps in China. Standardized and evidence-based pain management models are needed to address the needs of childhood cancer patients and complement the unique healthcare systems in China.

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References

1. Tutelman PR, Chambers CT, Stinson JN, et al. Pain in children with cancer: Prevalence, characteristics, and parent management. *Clin J Pain*. 2018; 34: 198.
2. Kuppenheimer WG, Brown RT. Painful procedures in pediatric cancer: A comparison of interventions. *Clin Psychol Rev*. 2002; 22: 753-786.
3. Twycross A, Parker R, Williams A, et al. Cancer-related pain and pain management: Sources, Prevalence, and the Experiences of Children and Parents. *J Pediatr Oncol Nurs*. 2015; 32: 369-384.
4. Matziou V, Vlachioti E, Megapanou E, et al. Perceptions of

- children and their parents about the pain experienced during their hospitalization and its impact on parents' quality of life. *Jpn J Clin Oncol*. 2016; 46: 862-870.
5. Hockenberry MJ, McCarthy K, Taylor O, et al. Managing painful procedures in children with cancer. *J Pediatr Hematol Oncol*. 2011; 33: 119-127.
 6. Mossey J. Defining racial and ethnic disparities in pain management. *Clin Orthop Relat Res*. 2011; 469: 1859-1870.
 7. Phelan SM, Hardeman RR. Health professionals' pain management decisions are influenced by their role (nurse or physician) and by patient gender, age and ethnicity. *Evid Based Nurs*. 2015; 18: 58.
 8. Brudvik C, Moutte S, Baste V, et al. A comparison of pain assessment by physicians, parents and children in an outpatient setting. *Emerg Med J*. 2017; 34: 138-144.
 9. Cote CJ, Wilson S. American Academy of Pediatrics, American Academy of Pediatric Dentistry Work Group on Sedation. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: An update. *Pediatrics*. 2006; 118: 2587.
 10. Godwin SA, Burton JH, Gerardo CJ, et al. Clinical policy: Procedural sedation and analgesia in the emergency department. *Ann Emerg Med*. 2014; 63: 258.
 11. Practice guidelines for moderate procedural sedation and analgesia 2018: A report by the American Society of Anesthesiologists Task Force on moderate procedural sedation and analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. *Anesthesiology*. 2018; 128: 437-479.
 12. Mahajan C, Dash HH. Procedural sedation and analgesia in pediatric patients. *J Pediatr Neurosci*. 2014; 9: 1-6.
 13. Wang Y, Liu Q, Yu J, et al. Perceptions of parents and paediatricians on pain induced by bone marrow aspiration and lumbar puncture among children with acute leukaemia: A qualitative study in China. *BMJ Open*. 2017; 7: 015727.
 14. Zhang S, Sun X. Achievements and challenges for childhood cancer in China. *Ann Transl Med*. 2015; 3: 366.
 15. Liu L, Wei K, Zhang X, et al. The current status and a new approach for chinese doctors to obtain medical knowledge using social media: A study of WeChat. *Wireless Communications and Mobile Computing*. 2018. Article ID 2329876.
 16. Wang T, Molassiotis A, Chung BPM, et al. Current research status of palliative care in mainland China. *J Palliat Care*. 2018; 33: 215-241.
 17. Li Y, Yu J, Tang L, et al. Cancer pain management at home: Voice from an underdeveloped region of China. *Cancer Nurs*. 2013; 36: 326-334.
 18. WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. Geneva: World health organization; 2012. available from: <https://www.ncbi.nlm.nih.gov/books/NBK138354/>.
 19. Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 2--clinical use. *Paediatr Anaesth*. 1997; 7: 93-101.
 20. Duedahl TH, Hansen EH. A qualitative systematic review of morphine treatment in children with postoperative pain. *Paediatr Anaesth*. 2007; 17: 756-774.
 21. Wong C, Lau E, Palozzi L, et al. Pain management in children: Part 2 — A transition from codeine to morphine for moderate to severe pain in children. *Can Pharm J (Ott)*. 2012; 145: 279.
 22. Yuen VM, Hui TW, Irwin MG, et al. Pediatric Sedation: The Asian Approach—Current State of Sedation in China. 2015 In: Mason K. (eds) *Pediatric Sedation Outside of the Operating Room*. Springer, New York, NY.
 23. Scarponi D, Pession A. Play therapy to control pain and suffering in paediatric oncology. *Front Pediatr*. 2016; 4: 132.
 24. Chotolli MR, Luize PB. Non-pharmacological approaches to control pediatric cancer pain: Nursing team view. *Revista Dor*. 2015; 16: 2.
 25. Li A, Montaña Z, Chen VJ, et al. Virtual reality and pain management: Current trends and future directions. *Pain Manag*. 2011; 1: 147-157.
 26. Yeung MT, Wong CL, Chan ON. Effects of immersive virtual reality on anxiety among paediatric cancer patients undergoing peripheral intravenous cannulation: Preliminary results of a pilot study. Paper presented at: The 8th Nursing Symposium on Cancer care. 2018; May: Hong Kong.
 27. Yu S, Wang J, Huang Y, et al. Managing pain in patients with cancer: The Chinese Good Pain Management Experience. *Journal of global oncology*. 2017; 3: 583-595.
 28. https://www.sohu.com/a/255870376_333130.