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Good Practice in Postoperative and Procedural Pain Management 2nd Edition, 2012

A Guideline from the Association of Paediatric Anaesthetists of Great Britain and Ireland

Endorsed by the British Pain Society, the Royal College of Nursing and the Royal College of Paediatrics and Child Health

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Section 1.0

Background

1.1 Introduction

This guidance was originally commissioned by the Association of Paediatric Anaesthetists of Great Britain and Ireland (APA). It is intended to be used by professionals involved in the acute care of children undergoing pain management after surgery or for painful medical procedures. It is designed to provide evidence-based information on the efficacy of analgesic strategies such that an informed choice of analgesics that are appropriate for the patient and clinical setting can be made. The document includes advice on the assessment of pain, a summary of current evidence for the efficacy of analgesic strategies, including evidence-based recommendations grouped according to named procedures, and a resume of analgesic pharmacology. This is the second edition of the guidelines – it was last published in 2008.

1.2 Guideline development committee

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1.3 Use, scope, and intention

This guidance was developed by a committee of health professionals with the assistance of a patient representative. It was published following a period of open public consultation, including advice from representatives from patient groups and professional organisations. It is intended for use by qualified heath professionals who are involved in the management of acute pain in children. In its present form, it is not suitable for use by other groups. At the present time, and largely because of resource limitations, no consumer guide is planned to enable the recommendations to be easily interpreted by those who do not already possess knowledge and training in the field of children's acute pain management.

The guidance is relevant to the management of children 0–18 years undergoing surgery or painful procedures in hospital settings. It includes recommendations for pain assessment, general principles of pain management, and advice on the use of pharmacological and nonpharmacological pain management strategies for specific medical and surgical procedures.

Procedures

The procedures are divided into two categories, painful diagnostic and therapeutic (Medical procedures; Section 4) and surgical procedures (Postoperative pain; Section 5). Guidance covers the management of acute pain *during* medical procedures and *after* surgery. It does not include advice on the intraoperative management of pain unless it is relevant to postoperative management or is otherwise stated, for example, the use of perioperative nerve blocks.

The procedures that have been included are not exhaustive and were selected by the committee because they are relatively commonplace and, or, because it was expected that there would be sufficient publications to allow recommendations to be made on the basis of an adequate level of evidence. For each procedure, there is a brief description, list of recommendations, and 'good practice points' followed by a discussion of the relevant published evidence including *Evidence tables* (see below) summarizing the level of evidence available for the efficacy individual analgesic strategies.

Evidence tables

Evidence tables are intended to allow the reader a rapid assessment of the strength of supporting evidence for individual analgesics or analgesic strategies relevant to the procedure in question. Evidence tabled as 'Direct' is that derived from studies that have specifically investigated the procedure in question. 'Indirect' evidence is derived from studies of procedures that the committee considered to be sufficiently similar, in terms of expected pain intensity, to allow extrapolation of evidence. Recommendations have not been formulated on the basis of indirect evidence.

1.4 Methodology and evidence grading, good practice points

Systematic methods were used to search for evidence. Electronic searches were performed on the published literature between January 2006 and December 2011. Search strategies including databases and keywords are described in detail in Appendix 1, the technical report. The bibliographies of meta-analyses, systematic reviews, and review articles published during this period were also scrutinized for relevant articles. Studies in English were included if they were directly relevant to the patient population and procedures. Abstracts were obtained to confirm inclusion or exclusion where necessary. Full text versions of included articles were obtained, a tabulated data extraction method was used to summarize the articles, and they were graded from 1 to 4 according to the criteria in Table 1.

Table 1 Criteria for assigning levels of evidence

Evidence levels	
1	1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias 1– Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2	2++ High quality systematic reviews of case–control or cohort studies. High quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal 2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal 2– Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Recommendations were formulated, where appropriate, and graded from A to D according to the criteria described in Table 2 using guidance published by the Scottish Intercollegiate Guidelines Network (SIGN), which are available at: http://www.sign.ac.uk/methodology/index.html and the National Institute of Clinical Evidence (NICE) http://guidance.nice.org.uk.

Table 2 Grading of recommendations

A	At least one meta analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice points indicate best practice based on the clinical experience and opinion of the guideline development committee but not necessarily supported by research evidence; they are provided in situations where published evidence is insufficient to make a formal recommendation but the committee wish to emphasize an important aspect of good practice.

1.5 Supplementary material

The following supplementary material is available for this guideline:

Appendix 1. Technical Report
Appendix 2. Implementation, cost effectiveness and audit
Appendix 3. Research implications

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supplementary materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

1.6 Contact information

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1.7 Conflicts of interest

Dr Richard Howard has acted as a Consultant and/or his department has received research or educational funding support from the following: Johnson and Johnson Pharmaceutical Research LLD, Grunenthal Ltd, Napp Pharmaceuticals Ltd and Wochardt UK Ltd. Dr Neil S. Morton is Editor-in-Chief, Pediatric Anesthesia and has received consultancy fees from AstraZeneca, Smith & Nephew and Schering-Plough. His department has received research funding from Abbott, AstraZeneca, Smith & Nephew and Carefusion (Alaris). The remaining members of the guideline development committee confirm that they have no conflicts of interest to declare.

Section 2.0

Executive Summary and Quick Reference Guide

Contents

2.1 Introduction

This evidence-based guideline for the management of postoperative and procedural pain in children was developed by a multidisciplinary guideline development group of the Association of Paediatric Anaesthetists of Great Britain and Ireland with representation from consumers, the Royal College of Paediatrics and Child Health (RCPCH), the British Pain Society (BPS), the Royal College of Nursing (RCN) and the Faculty of Pain Medicine of the Royal College of Anaesthetists (FPMRCA). The guideline was complied using methodology developed by the Scottish Intercollegiate Guideline Network (SIGN). Descriptions of levels of evidence, grading of recommendations and their associated symbols can be found in Section 1.0 and in the technical report, Appendix 1, of the supplementary materials. The guideline was developed for the use of health professionals. It is intended to inform decision making in the management of acute postoperative and procedural pain. This is the second edition of the guideline, it supersedes previous versions. The guideline will be updated every 5 years.

The guideline comprises evidence-based **'Recommendations'** and '*Good practice points*'. Recommendations are graded A–D according to the strength of evidence underpinning them, the grading does not reflect the importance of the recommendation. *Good practice points* indicate best practice according to the clinical experience and opinion of the guideline development committee.

Not all recommendations are included in this quick reference guide, common abbreviations and complete details are available in the relevant sections of the guideline.

2.2 Pain assessment

Pain assessment and measurement of pain intensity are vital components of good pain management practice. Self-report of pain by children who are able to do so, observation of behaviors or physiological parameters that are known to reflect pain intensity using a standardized pain 'measure', 'instrument', or 'tool' are options. To select an appropriate method, the principles and limitations of standardized pain measures must be understood.

A simple guide to valid measures for postoperative and procedural pain is given in Table 1. But please note that reliance on chronological age as the sole indicator of a child's capacity to self-report will inevitably generate both false positives (invalid scores from children who do not understand the scale) and false negatives (not obtaining valid scores from children who do understand the scale but were not asked).

Table 1 Recommended measures for procedural and postoperative pain assessment as a function of the child's chronological age

Child's age*	Measure
Newborn–3 years old	COMFORT or FLACC
4 years old	FPS-R + COMFORT or FLACC
5–7 years old	FPS-R
7 years old +	VAS or NRS or FPS-R

*With normal or assumed normal cognitive development

Good practice points

To assess pain, effective communication should occur between the child whenever feasible, their family or carers, and the professionals in the multi-disciplinary team.

Standardized instruments should be used in their final validated form. Even minor modifications that alter the psychometric properties of the tool may bias clinical assessments and render comparison between studies invalid.

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Recommendations

Children's self-report of their pain is the preferred approach: Grade B

No individual measure can be broadly recommended for pain assessment across all children or all contexts: Grade B

An observational measure should be used in conjunction with self-report with 3–5-year-olds as there is limited evidence for the reliability and validity of self-report measures of pain intensity in this age group: Grade B

2.3 Medical procedures

Routine medical care involving blood sampling and other painful diagnostic and therapeutic procedures can cause great distress for children and their families. When such procedures are essential, it is important that they should be achieved with as little pain as possible. There are 10 general considerations to remember prior to planning the management of a painful procedure: see Box 1.

Box 1: Planning a painful procedure

1. Infants and children of all ages, including premature neonates, are capable of feeling pain and require analgesia for painful procedures.
2. Developmental differences in the response to pain and analgesic efficacy should be considered when planning analgesia.
3. Consider whether the planned procedure is necessary, and how the information it will provide might influence care? Avoid multiple procedures if possible.
4. Plan the timing of procedures to minimize the frequency of a painful procedure.
5. Is sedation or even general anesthesia likely to be required for a safe and satisfactory outcome?
6. Would modification of the procedure reduce pain? For example, venepuncture is less painful than heel lance for blood sampling in infants.
7. Is the planned environment suitable? Ideally, this should be a quiet, calm place with suitable toys and distractions.
8. Ensure that appropriate personnel who possess the necessary skills are available, enlist experienced help when necessary.
9. Allow sufficient time for analgesic drugs and other analgesic measures to be effective.
10. Formulate a clear plan of action should the procedure fail or pain become unmanageable using the techniques selected.

Good practice points

Pain management for procedures should include both pharmacological and nonpharmacological strategies whenever possible.

Children and their parents/carers benefit from psychological preparation prior to painful procedures.

2.4 Procedural pain in the neonate: general recommendations

Breast-feeding should be encouraged during the procedure, if feasible: Grade A

Nonpharmacological measures including nonnutritive sucking, 'kangaroo care', swaddling/facilitated tucking, tactile stimulation, and heel massage can be used for brief procedures: Grade A

2.5 Procedural pain in the neonate: specific recommendations

2.5.1 Blood Sampling including percutaneous central venous catheter insertion

Sucrose or other sweet solutions can be used: Grade A
Venepuncture (by a trained practitioner) is preferred to heel lance for larger samples as it is less painful: Grade A

Topical local anesthetics can be used for venepuncture pain: Grade B

Nonpharmacological measures including tactile stimulation, breast-feeding, nonnutritive sucking, 'kangaroo care', and massage of the heel can be used for heelprick blood sampling: Grade A

Topical local anesthetics alone are insufficient for heel lance pain: Grade A

Using the whole plantar surface of the heel reduces the pain of heelprick blood sampling: Grade B

Topical tetracaine plus morphine is superior to topical analgesia alone for CVC insertion pain in ventilated infants: Grade B

2.5.2 Ocular examination for retinopathy of prematurity (ROP)

Sucrose may contribute to pain response reduction in examination for retinopathy: Grade A

Infants undergoing examination for retinopathy should receive local anesthetic drops in combination with other measures if an eyelid speculum is used: Grade B

Swaddling, developmental care, nonnutritive sucking, pacifier should be considered for neonates undergoing examination for retinopathy: Grade B

2.5.3 Lumbar puncture

Topical local anesthesia is effective in reducing LP pain: Grade A

2.5.4 Urine sampling

Transurethral catheterization with local anesthetic gel is preferred as it is less painful than suprapubic catheterization with topical local anesthesia: Grade B

Sucrose reduces the pain response to urethral catheterization: Grade C

2.5.5 Chest drain (tube) insertion and removal

See older children below

2.5.6 Nasogastric tube placement (See also; older children, below)

Sucrose can reduce the pain response from NGT insertion: Grade B

2.5.7 Immunization and intramuscular injection

Swaddling, breast-feeding or pacifier, and sucrose should be considered in neonates undergoing vaccination: Grade A

2.6 Procedural pain in older children

This section includes all infants and children outside the neonatal period. Painful procedures are often identified as the most feared and distressing component of medical care for children and their families. When managing procedural pain in infants, older children and adolescents special emphasis should given not only to proven analgesic strategies but also to reduction in anticipatory and procedural anxiety by suitable preparatory measures. Families, play therapists, nursing staff and other team members play key roles in reducing anxiety by suitable preparation.

Specific Recommendations

2.6.1 Blood sampling and intravenous cannulation

Topical local anesthesia should be used for intravenous cannulation: Grade A

Psychological strategies, for example, distraction or hypnosis, to reduce pain and anxiety should be used: Grade A

2.6.2 Lumbar puncture

Behavioral techniques of pain management should be used to reduce LP pain: Grade A

Topical LA and LA infiltration are effective for LP pain and do not decrease success rates: Grade B

50% nitrous oxide in oxygen should be offered to children willing and able to cooperate: Grade C

2.6.3 Chest drain (tube) insertion and removal

There is little published evidence looking at analgesic options for chest drain insertion or removal.

Good practice points

For chest drain insertion, consider general anesthesia or sedation combined with subcutaneous infiltration of buffered lidocaine. Selection of appropriate drain type may reduce pain by facilitating easy insertion.

For chest drain removal, consider a combination of two or more strategies known to be effective for painful procedures such as psychological interventions, sucrose or pacifier (in neonates), opioids, nitrous oxide, and NSAIDs

2.6.4 Bladder catheterization and related urine sampling procedures

Psychological preparation and psychological and behavioral interventions should be used during bladder catheterization and invasive investigations of the renal tract: Grade B

Infants: consider procedure modification as urethral catheterization is less painful than SPA for urine sampling: Grade B

2.6.5 Insertion of nasogastric tubes

Good practice point

Topical local anesthetics such as lidocaine containing lubricant gel applied prior to placement are likely to reduce the pain and discomfort of NGT insertion.

2.6.6 Immunization and intramuscular injection

Psychological strategies such as distraction should be used for infants and children undergoing vaccination: Grade A

Consider additional procedure modifications such as vaccine formulation, order of vaccines (least painful first) needle size, depth of injection (25–mm, 25-gauge needle) or the use of vapocoolant spay: Grade A

Swaddling, breast-feeding or pacifier, and sucrose should be considered in infants undergoing vaccination: Grade A

2.6.7 Repair of lacerations

For repair of simple low-tension lacerations, tissue adhesives should be considered as they are less painful, quick to use, and have a similar cosmetic outcome to sutures or adhesive skin closures (steri-strips): Grade A

Topical anesthetic preparations, for example, LAT (lidocaine–adrenaline–tetracaine) if available, can be used in preference to injected LA, as they are less painful to apply; it is not necessary to use a preparation containing cocaine: Grade A

Buffering injected lidocaine with sodium bicarbonate should be considered: Grade A

'HAT' should be considered for scalp lacerations. It is less painful than suturing, does not require shaving, and produces a similar outcome: Grade B

If injected lidocaine is used, pretreatment of the wound with a topical anesthetic preparation, for example, lidocaine–adrenaline–tetracaine (LAT) gel reduces the pain of subsequent injection: Grade B

50% nitrous oxide reduces pain and anxiety during laceration repair: Grade B

2.6.8 Change of dressings in children with burns

Potent opioid analgesia given by oral, transmucosal, or nasal routes according to patient preference and availability of suitable preparations should be considered for dressing changes in burned children: Grade A

Nonpharmacological therapies such as distraction and relaxation should be considered as part of pain management for dressing changes in burned children: Grade B

2.6.9 Botulinum injections for children with muscle spasm

Good practice point
50% Nitrous oxide/oxygen should be considered in children who are able to cooperate with self-administration.

2.7 Postoperative pain

Postoperative care is frequently shared between heath professionals from different disciplines: they should understand the general principles of pain assessment and pain management in children. Postoperative analgesia should be planned and organized *prior to surgery* in consultation with patients and their families or carers, and other members of the perioperative team.

Good practice points
Providers of postoperative care should understand the general principles of good pain management in children; this includes knowledge of assessment techniques and the use of analgesics at different developmental ages.

Pediatric anesthetists are responsible for initiating postoperative analgesia. They should liaise with patients and their families/carers, surgeons, and other members of the team providing postoperative care to ensure that pain is assessed, and suitable ongoing analgesia is administered.

Postoperative analgesia should be appropriate to developmental age, surgical procedure, and clinical setting to provide safe, sufficiently potent, and flexible pain relief with a low incidence of side effects.

Combinations of analgesics should be used unless there are specific contraindications, for example; local anesthetics, opioids, NSAIDs, and paracetamol can be given in conjunction, not exceeding maximum recommended dose.

Recommendations

2.7.1 ENT surgery

Myringotomy
Oral paracetamol or NSAIDS (ibuprofen, diclofenac, or ketorolac) in suitable doses can achieve adequate early postoperative analgesia: Grade B

Opioids are effective but not recommended for routine use because of side effects: Grade B

Tonsillectomy
A combination of individually titrated intraoperative opioids, dexamethasone, and regularly administered perioperative mild analgesics (NSAIDS and /or paracetamol) is recommended for management of tonsillectomy pain: Grade A

Topical application or injection of local anesthetic in the tonsillar fossa improves early pain scores following tonsillectomy: Grade A

Implementation of standardized protocols including intraoperative opioid ± anti-emetic, perioperative NSAID (diclofenac or ibuprofen) and paracetamol are associated with acceptable pain relief and low rates of PONV: Grade C

Mastoid and middle ear surgery
Great auricular nerve block can provide similar analgesia and reduced PONV compared with morphine. Preincision timing of the block confers no additional benefit: Grade B

2.7.2 Opthalmology

Strabismus surgery

Intraoperative LA blocks (subtenon's or peribulbar) reduce PONV and may improve perioperative analgesia in comparison with IV opioid but provide no benefit over topical LA: Grade B

Topical NSAIDS do not improve pain scores or postoperative analgesic requirements when compared with topical LA or placebo: Grade B

Intraoperative opioid and NSAID provide similar postoperative analgesia but opioid use is associated with increased PONV: Grade B

Vitreoretinal surgery

In vitreoretinal surgery NSAID can provide similar analgesia but lower rates of PONV compared with opioid: Grade C

Peribulbar block improves early analgesia and may reduce PONV compared with opioid: Grade C

2.7.3 Dental procedures

NSAIDS with or without paracetamol reduce pain following dental extractions: Grade B

Swabs soaked with bupivacaine on exposed tooth sockets following extraction produce no or minor improvements in pain in the immediate postoperative period: Grade B

Intraoperative LA infiltration reduces postoperative pain following dental extractions, but provides little additional benefit over NSAIDS and paracetamol alone: Grade B

2.7.4 General surgery and urology (minor and intermediate)

Sub-umbilical surgery

LA should be used when feasible: wound infiltration, transversus abdominis plane (TAP) block, ilio-inguinal nerve block and caudal analgesia are effective in the early postoperative period following sub-umbilical surgery: Grade A

Circumcision

Caudal epidural and dorsal nerve block are effective in the early postoperative period, with low rates of complications and side effects: Grade A

Neonatal circumcision

LA should be used as it is superior to other techniques for circumcision pain: Grade A

Dorsal nerve block is more effective than subcutaneous ring block or topical LA: Grade A

When using topical local anesthetic it must be applied correctly and sufficient time allowed for it to become effective: Grade A

Hypospadias repair

LA central neuraxial or dorsal nerve block is effective reducing the need for postoperative supplementary opioid administration following hypospadias surgery: Grade A

Orchidopexy

Caudal block is effective in the early postoperative period for orchidopexy with low rates of complications and side effects: Grade A

Open inguinal hernia repair

LA wound infiltration, ilio-inguinal nerve block, paravertebral block or caudal analgesia are effective in the early postoperative period: Grade A

2.7.5 General surgery and urology (Major)

Major intra-abdominal surgery

Intravenous opioids either as continuous infusion, NCA, or PCA are effective following major abdominal surgery: Grade A

Epidural analgesia with LA should be considered for major abdominal surgery. The addition of neuraxial clonidine or opioid may further improve analgesia but side effects may also be increased: Grade B

Appendicectomy (open)

PCA combined with NSAID is effective for postappendicectomy pain: Grade B

Fundoplication (open)

Epidural LA + opioid is effective and may be associated with improved clinical outcome in selected patients following fundoplication: grade D

2.7.6 Laparoscopic surgery

Good practice points

Infiltration of port sites with LA as part of a multimodal analgesic strategy may reduce postoperative pain following laparoscopy.

Although overall postoperative analgesic requirements appear to be reduced following laparoscopy, pain may be equivalent to the equivalent open procedure in some circumstances, particularly during the first 24 h.

2.7.7 Orthopaedics, spinal and plastic surgery

Good practice point

There is no evidence from studies in children that NSAIDs have a deleterious effect on bone fusion. The analgesic benefit of short-term NSAID use has been demonstrated and may frequently outweigh any hypothetical risk.

Lower limb surgery

Peripheral nerve blocks provide superior analgesia and are associated with fewer adverse effects compared with intravenous opioids: Grade B

Continuous peripheral nerve blocks are feasible, effective and safe, and are associated with lower pain scores: Grade B

Epidural opioids are effective, reduce the dose requirements of local anesthetic, and rescue IV opioids but increase the incidence of side effects: Grade B

Epidural techniques are associated with lower pain scores than intravenous opioid analgesia: Grade C

Systemic paracetamol and NSAID reduce intravenous opioid requirements: Grade C

Upper Limb Surgery

Brachial plexus blocks provide satisfactory analgesia for hand and forearm surgery extending into the postoperative period: Grade B

The axillary, infraclavicular, supraclavicular, and interscalene approach are feasible and effective: Grade B

Spinal surgery

Epidural techniques produce a modest improvement in pain control, compared with intravenous opioids in patients undergoing corrective surgery for adolescent idiopathic scoliosis: Grade B

Intrathecal opioids decrease intra-operative blood loss and IV opioid consumption postoperatively. The duration of action is 18–24 h: Grade C

Dual catheter epidural techniques should be considered, as this permits coverage of multiple spinal levels: Grade C

The use of LA + lipophilic opioid in the epidural space with a single epidural catheter does not show an analgesic benefit over intravenous opioid techniques: Grade C

The use of LA + hydrophilic opioids in the epidural space has a favorable analgesic profile compared with IV opioid, but at the expense of increased adverse effects: Grade D

Cleft lip and palate and related procedures of head and neck

Infraorbital nerve block provides effective analgesia for cleft lip repair in the early postoperative period: Grade A

2.7.8 Cardiothoracic surgery

Cardiac surgery (sternotomy)

Epidural and intrathecal techniques with opioid and/or LA are effective for sternotomy pain but only marginal benefits have been demonstrated, and there is insufficient data concerning the incidence of serious complications: Grade B

Thoracotomy

Epidural analgesia is effective for post-thoracotomy pain: Grade D

2.7.9 Neurosurgery

Craniotomy and major neurosurgery

Good practice point

Analgesia following neurosurgery requires good communication and close cooperation between members of the perioperative team. Frequent pain assessments should be a routine part of postoperative care. A multimodal analgesic approach is suitable, which may include the use of LA infiltration, paracetamol, NSAID (when not contraindicated), and parenteral or oral opioid as determined by assessed analgesic requirements.

Section 3.0
Pain Assessment

Contents

Children's pain should be assessed. Effective pain assessment is essential both in terms of its contribution to the prevention and relief of a child's pain (1–4) and also in its role as a diagnostic aid. The centrality of pain assessment to high-quality pain management is enshrined in many current pain management recommendations, position statements, reports, and guidelines (5–9).

Assessment refers to a broad endeavor aiming to identify the factors that shape the pain experience including physiological, cognitive, affective, behavioral and contextual, and their dynamic interactions.

Measurement refers to the application of a metric on one aspect of pain, usually intensity. This guideline focuses primarily on pain measurement assuming that the appropriate pain assessment as per clinical practice takes place.

Table 1 Evaluation criteria for IMMPACT reviews (12)

	Criteria for categories
I. A well-established assessment	The measure must have been presented in at least 2 peer-reviewed articles by different investigators or investigatory teams. Sufficient detail about the measure to allow critical evaluation and replication. Detailed information indicating good validity and reliability in at least 1 peer-reviewed article.
II. Approaching well-established assessment	The measure must have been presented in at least 2 peer-reviewed articles, which might be by the same investigator or investigatory team. Sufficient detail about the measure to allow critical evaluation and replication. Validity and reliability information either presented in vague terms (e.g., no statistics presented) or only moderate values presented.
III. Promising assessment	The measure must have been presented in at least 1 peer-reviewed article. Sufficient detail about the measure to allow critical evaluation and replication. Validity and reliability information either presented in vague terms or only moderate values presented.

Existing guidelines: An evidence-based guideline 'The Recognition and Assessment of Pain in Children was first produced by the Royal College of Nursing (RCN), UK, in 1999 and was revised in 2009 (10). The RCN guideline was endorsed in 2001 by the Royal College of Paediatrics and Child Health that produced 'Guidelines for Good Practice' (11), which were the recommendations based on the original RCN guideline. We suggest that both these documents be consulted for further and more detailed information; the evidence and recommendations presented here are intended to support and supplement this existing guidance.

Technical note for this section of the guideline: in addition to the SIGN criteria, and in line with current practice, instruments were also evaluated based on a set of evaluation criteria for the assessment of quality of evidence for IMMPACT reviews (12) (see Table 1, and Appendix 1, Technical Report for further information).

3.1 General principles of pain assessment

Good pain assessment contributes to the prevention and/or early recognition of pain as well as the effective management of pain (1,4). There are three fundamental approaches to pain assessment in children:

Self-report: measuring expressed experience of pain.

Observational/Behavioral: measuring behavioral distress associated with pain or measuring the perceived experience of pain by parent or carer report.

Physiological: primarily measuring physiological arousal consequent to pain

As self-report is the only truly direct measure of pain, it is often considered the 'gold standard' of measurement. However, for developmental reasons, self-report may be difficult or impossible in some children and therefore a proxy measure must be used. For pain to be measured as accurately as possible, the principles underpinning assessment at different developmental ages and in different settings must be appreciated.

Good practice points

Children's pain should be assessed, documented, and appropriate action taken. This requires both training of healthcare professionals in pain assessment and measurement with standardized instruments.

In order to assess pain, effective communication should occur between the child whenever feasible, their family or carers, and the professionals in the multidisciplinary team.

Standardized instruments should be used in their final validated form. Even minor modifications alter the psychometric properties of the tool and render comparisons between studies invalid and clinical assessment biased.

Recommendations

No individual measure can be broadly recommended for pain assessment across all children or all contexts: Grade B (12–14).

Children's self-report of their pain, is the preferred approach, where feasible: Grade B (13).

An observational measure should be used in conjunction with self-report with 3–5 year olds as there is limited evidence for the reliability and validity of self-report measures of pain intensity in this age group: Grade B (15).

Sole use of physiological measures in clinical practice is unproven and therefore not recommended: Grade D (16,17).

Evidence

The results of pain assessment must be documented, acted upon, reassessed, and re-evaluated to determine the effectiveness of interventions (1,18–21). Improved documentation can result in improved pain management (22–25). Studies demonstrate that there is low utilization of pain tools and policies (26) and that pain is under-assessed (3,27) and poorly documented (28,29), resulting in children being under-medicated and/or their pain being poorly managed (3,27,30–32). Regular pain evaluation can contribute to the safety and efficacy of the management of acute pain (33).

Self-report: Pain is a highly complex and multidimensional experience, and pain intensity scores are a necessary oversimplification. Children's self-report of pain is regarded as the gold standard, and in most circumstances, it is the preferred approach. Children's self-report of pain may differ to that of their parents or the nurse caring for them (34). However, it must also be recognized that self-report in both children and adults is complex (13,35), dependent upon age and/or level of cognition (36), affected by a range of social and other influences (37–39), and is subject to biases (15,37,40).

Nevertheless, although children's subjective reports of pain are probably the best way of documenting the presence and intensity of pain, it requires quite advanced cognitive skills (including classification, seriation, and matching) for children to be able to provide reliable and valid self-reports of pain intensity. Faces scales may not require the ability to seriate or estimate quantities because the task can be handled by matching how one feels to one of the faces, which is presumed to be easier than quantitative estimation (41). However, self-report is subject to individual response biases, reflecting the person's appraisal of the consequences of the pain report (36). Although children of preschool age are often asked to confirm or deny that they are feeling internal states such as hunger or thirst, they are rarely, if at all, asked to make quantitative estimates of these states. Thus, using a self-report pain scale is an unusual experience for most young children (15). Alternative strategies for answering confusing questions are frequently adopted by young children. Response bias is a propensity to respond systematically to test items in ways unrelated to the item content. Response biases that have been documented in the pediatric literature include:

- Anchor effects which refer to the influence of surrounding conditions or prior experience on the estimation of a quantity. For example, pain ratings on faces scales are influenced by whether the lower anchor face is smiling or not.

- Sequence bias such as the child selecting (for example) the leftmost face to answer the first question, and then picks the adjacent face to the right in response to each successive question, in a sequence of responses that would be scored in an ascending or descending series (e.g., 0–2–4–6–8).

- Giving the same answer to all questions (15,42–44). In experimental situations where children were asked to rate hypothetical pain situations, it has been demonstrated that young children from four to seven cannot distinguish as many faces as proposed by the majority of available faces scales (45). These results strongly recommend a reduction in the number of response levels of faces scales for pain assessment in children.

It should be noted that not all inaccurate responses indicate the occurrence of response biases as inaccurate responses can occur for other reasons such as failure to understand the question, deliberate random or incorrect responding, lack of motivation and attention to the task, or undetected learning or cognitive difficulties (15). Clinicians should be aware that young children's pain scores can be misleading, particularly when a pain scale is used only once to measure pain on a single occasion, making it difficult for the clinician to detect any underlying response bias. Therefore, self-report pain scores from children below 5 years of age should generally be treated with caution and should be corroborated by observational measures.

Choice of assessment tool: No individual observational (14), self-report (13), or physiological measure is broadly recommended for pain assessment across all children or all contexts. Some validated pain measures, primarily developed for use within pain research studies, do not transition easily in everyday practice as they can be challenging to use in clinical settings (46). Therefore, healthcare professionals need to make informed choices about which tool to use to assess each individual child's pain. Composite measures using self-report and at least one other measure may be a better approach (13). Table 3 provides guidance, as a function of a child's chronological age, on measures that have good psychometric properties and can be used for the assessment of procedural and postoperative pain.

Education: Healthcare professionals require appropriate levels of education about pain (27,47–49). They also need adequate training/preparation in the use of pain assessment tools and proficiency in using them (23,50,51). Improved working practices (52), organizational commitment (23), quality improvement strategies (23), and one-to-one coaching (53) have been shown to enhance pain assessment. Studies have demonstrated that health professionals' assessment of children's pain is subject to a range of individual, social, and contextual influences (54–57). Professionals need to be flexible and willing to develop more positive attitudes and beliefs regarding the attributes of children's pain (19). Perceptions about the pain experienced by particular groups of children, such as children with neurological impairment may need to be challenged (58,59).

Parents and other carers should also be given appropriate information about their child's pain (55,60–62) and emotional support and clarification of their role in their child's pain (61,63). Their beliefs about their child's pain need to be taken into consideration as these beliefs may impact their child's care. Parents/carers of children with cognitive impairment may have mistaken beliefs about their child's pain, which need to be carefully explored (59). Parents/carers also need appropriate information and teaching in the use of pain assessment tools if they are to be effective in assessing and managing their child's pain (59,63,64).

Table 2 Recommended measures for procedural and postoperative pain assessment as a function of the child's chronological age

Child's age*	Measure
Newborn–3 years old	COMFORT or FLACC
4 years old	FPS-R + COMFORT or FLACC
5–7 years old	FPS-R
7 years old +	VAS or NRS or FPS-R

*with normal or assumed normal cognitive development
Note: Reliance on chronological age as the sole indicator of a child's capacity to self-report will inevitably generate both false positives (invalid scores from children who do not understand the scale) and false negatives (not obtaining valid scores from children who do understand the scale but were not asked).

3.2 Pain measurement tools

A bewildering number of acute pain measurement tools exist. Tools vary in relation to three broad groups of factors: child-related, user-related, and structural. For example, the age, cognitive level, language, ethnic/cultural background of the child, the setting for which they are to be used, and the tool's psychometric properties (e.g., validity and reliability) in that context (13,14,35,65–67). Such factors should be taken into consideration when making choices about which acute pain measurement tool to use.

Despite the proliferation and availability of tools, they are not always used consistently or well (68–70) and inconsistencies have been identified between reported assessment practice and documented practice (3,26,27,29,71).

The following provides a brief guide to some of the best evaluated and commonly used tools in current clinical practice. The tools are broadly divided into self-report and observational/behavioral tools and then further subdivided into their suitability for type of pain (acute procedural, postoperative, or disease-related) and/or setting. Brief information of the *intended* age ranges for which the tool has been developed and/or information on the ages for which the tool has been validated are presented (look at the data extraction tables for more information on each measure's psychometric properties and relevant studies).

3.2.1 Self-report tools (5 years and above)

The most psychometrically sound and feasible self-report tools, based on age/developmental level and type of pain, have been recommended for use in clinical trials (marked * below) (13). However, other tools, while not necessarily suitable for clinical trials, have been shown to have good clinical utility and have been validated.

Procedural pain

- Wong and Baker FACES Pain Scale (72): intended for 3–18 year olds.
- Faces Pain Scale-Revised* (44): see also (43,73): intended for 4–12 year olds.

- Visual analogue* and numerical rating scales: intended for 8 years plus.
- Pieces of Hurt Tool* (74), see also (75), intended for 3–8 year olds.
- MSPCT (The Multiple Size Poker Chip Tool) (76), intended for 4–6 year olds.

Postoperative pain

- Wong and Baker FACES Pain Scale (72): intended for 3–18 year olds.
- Faces Pain Scale-Revised* (44), see also (43,73), intended for 4–12 year olds.
- Visual analogue* and numerical rating scales: intended for 8 years plus.
- Pieces of Hurt Tool* (74) see also (75), intended for 3–8 year olds.

Disease-related pain

- Wong and Baker FACES Pain Scale (72): intended for 3–18 year olds.
- Faces Pain Scale-Revised (44), see also (43,73): intended for 4–12 year olds.
- Visual analogue and numerical rating scales: intended for 8 year olds and older.

3.2.2 *Observational/behavioral measures*

Pain and pain-related distress cannot be easily separated either conceptually or at a practical level; for example, cry and scream can be the indicative of fear or pain. Therefore, each of the scales below should be viewed as a measure of pain and distress, regardless of the title of the scale (77).

A. Premature infants and neonates

Not all neonatal pain assessment tools have been rigorously tested for construct validity, feasibility, and clinical utility (78). However, the following tools are widely used for neonatal pain assessment and used within neonatal intensive care/special care baby units.

Acute procedural pain

- PIPP (Premature Infant Pain Profile) (79): See also (80,81).
- CRIES (82).
- NFCS (Neonatal Facial Coding Scale) (83,84).

Postoperative pain

- PIPP (Premature Infant Pain Profile) (79): see also (85).
- CRIES (82): see also (85).
- COMFORT scale (86–88).

B. Children and young people without cognitive impairment

On the basis of the highest evidence of validity, reliability, and clinical utility and use within practice settings, the following behavioral tools can be recommended for children and young people without cognitive impairment aged 3–18 years in the following specific situations (14).

Procedural pain

- FLACC (Face, Legs, Arms, Cry, and Consolability) (89); see also (50,90–92): intended for 1–18 year olds.
- CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) (93); see also (94): intended for 1–18 year olds.

Postoperative pain (in the hospital setting)

- FLACC (89): intended for 1–18 year olds.

Postoperative pain (being managed by parents/carers at home)

- PPPM (Parents Postoperative Pain Measure) (95); see also (96,97): intended for 1–12 year olds.

Pain in the critical care setting

- COMFORT scale (86): intended for newborn–17 year olds.

C. Children and young people with cognitive impairment

While there is less substantive evidence of reliability, validity, clinical utility, and widespread use within practice settings, the following tools are suitable for use with children and young people with cognitive impairment in the following situations:

Procedural/disease-related pain

- NCCPC-R (Non-Communicating Children's Pain Checklist) (59,98–100): intended for 3–18 year olds
- PPP (The Pediatric Pain Profile) (101): See also (102): intended for 1–18 year olds.

Postoperative pain

- NCCPC-PV (Non-Communicating Children's Pain Checklist – Postoperative Version) (100): intended for 3–19 year olds.
- PPP (The Pediatric Pain Profile) (101): intended for 1–18 year olds.
- Revised FLACC (50): intended for 4–19 year olds.

Parent report of their child's postoperative pain intensity

The most psychometrically sound and feasible parent report tool, based on age/developmental level and type of pain, has been recommended for use in clinical trials (13). However, this may not necessarily directly transfer to clinical utility and more research is needed.

- PPPM (Parents Postoperative Pain Measure) (95); see also (96,97).

3.2.3 *Physiological measures*

Physiological parameters such as heart rate variability, skin conductance, and changes in salivary cortisol can be used indirectly to indicate the presence of pain (103–106). However, blood pressure, heart rate, and respiratory rate have been shown to be unreliable indicators in newborns, infants, and young children with wide inter-individual behavior–physiology correlations after major surgery in 0–3-year-old infants (16). More recently, the magnitude of evoked cortical activity has been suggested as a possible indicator of pain (107). While the method appears promising and correlations with other pain measures have been found to be good, similarly to the measurement of other physiological parameters such as cortisol changes, it has limited clinical utility. It is questionable whether the pain experience can be meaningfully reduced to physiological activation alone; therefore, physiological measures should be used in conjunction with other tools/measures to determine the presence and intensity of pain.

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Section 4.0
Medical Procedures

Contents

4.1 General considerations

Routine medical care involving blood sampling and other painful diagnostic and therapeutic procedures can cause great distress for children and their families. When such procedures are essential, it is important that they should be achieved with as little pain as possible. For many children who have chronic illness, these procedures often need to be repeated, and this can generate very high levels of anxiety and distress if their previous experience has been poor. The 10 general principles, which apply to the management of all procedures at any age, are listed below. Further advice for use in specific age-groups, and specifically for some of the most common procedures, is described in sections 4.2 and 4.3.

1. Infants and children of all ages, including premature neonates, are capable of feeling pain and require analgesia for painful procedures.

2. Developmental differences in the response to pain and analgesic efficacy should be considered when planning analgesia.

3. Consider whether the planned procedure is necessary, and how the information it will provide might influence care? Avoid multiple procedures if possible.

4. Plan the timing of procedures to minimize the frequency of a painful procedure.

5. Are sedation or even general anesthesia likely to be required for a safe and satisfactory outcome?

6. Would modification of the procedure reduce pain? For example, venepuncture is less painful than heel lance.

7. Is the planned environment suitable? Ideally, this should be a quiet, calm place with suitable toys and distractions.

8. Ensure that appropriate personnel who possess the necessary skills are available, and enlist experienced help when necessary.

9. Allow sufficient time for analgesic drugs and other analgesic measures to be effective.

10. Formulate a clear plan of action should the procedure fail or pain become unmanageable using the techniques selected.

Good practice point

Pain management for procedures should include both pharmacological and nonpharmacological strategies whenever possible.

4.2 Procedural pain in the neonate

Premature neonates are able to perceive pain, but the response to both pain and analgesia is dependant on developmental age. Because of this, pain assessment in this age-group is particularly difficult (see section 3), and the low sensitivity of many pain measurement tools can complicate the interpretation of evidence. Clinically, neonates appear to be sensitive to the adverse effects of many drugs, including analgesics;

however, reductions in the response to pain have been observed following nontraditional analgesia such as sucrose and physical and environmental measures, for example, suckling or tactile stimulation, which are currently not known to have potentially harmful effects. A number of documents including reviews, guideline, and policy statements have been published recently on the subject of procedural pain management in the neonate (1–4). On the basis of the currently available evidence, the following measures can be *generally* recommended for the management of procedural pain in the neonate:

Recommendations

Breast-feeding should be encouraged during the procedure, if feasible: Grade A (5–9).

Nonpharmacological measures including non-nutritive sucking, 'kangaroo care', swaddling/facilitated tucking, tactile stimulation, and heel massage can be used for brief procedures: Grade A (5,6,10–30).

4.2.1 Blood sampling in the neonate (includes peripheral venous, arterial, and percutaneous central venous cannulation)

Blood sampling is a necessary and routine part of neonatal care. Where an indwelling arterial catheter is not available, then venepuncture (VP) or heel prick blood sampling (HPBS) is used. All newborn babies in the UK have a HPBS as part of the UK screening regime. Neonates admitted to intensive care or who are cared for on postnatal wards will require frequent blood sampling that has been identified in many studies as a significant cause of pain and morbidity. HPBS requires appropriate training and is used to collect small blood samples such as blood glucose, bilirubin newborn screening tests, and capillary blood gases. VP also requires training but is technically more difficult and is used to collect larger blood samples. The principles and techniques of pain relief are applicable to other invasive procedures such as peripheral arterial line insertion and percutaneous central venous catheters (i.e., long line). Please also see sections 4.0 and 4.1 on the general management of procedural pain.

Recommendations

Sucrose or other sweet solutions can be used: Grade A (5,6,10–18,22,29,31–40).

Nonpharmacological measures including tactile stimulation, breast-feeding, non-nutritive sucking, 'kangaroo care', and massage of the heel can be used for heel prick blood sampling: Grade A (12,19–28,30).

Venepuncture (by a trained practitioner) is preferred to heel lance for larger samples as it is less painful: Grade A (18,41–43).

Topical local anesthetics alone are insufficient for heel lance pain: Grade A (44,45).

Topical local anesthetics can be used for venepuncture pain: Grade B (44–47).

Using the whole plantar surface of the heel reduces the pain of heel prick blood sampling: Grade B (48,49).

Remifentanil and sucrose decreased central venous catheter pain: Grade B: (36).

Topical tetracaine plus morphine is superior to topical analgesia alone for central venous catheter pain in ventilated infants: Grade B (50,51).

Evidence

A large number of studies have demonstrated that sucrose before VP or HPBS reduces the behavioral pain scores measured by a range of validated assessments (5,6,10–18,22,29,31–40,52). The dose of sucrose differed across these studies.

Relieving the pain of HPBS has been challenging with pharmacological methods. However, nonpharmacological methods including breast-feeding, non-nutritive sucking, kangaroo care, and premassage of the heel before and during HPBS have consistently demonstrated reduced behavioral pain scores and physiological markers (12,19–28).

VP appears to be less painful than HPBS so is the preferred option whenever practical (18,41,43). Topical local anesthesia (LA) can reduce the pain of VP and insertion of central venous catheters (44–46,51,53). However, topical LA is not effective for HPBS (45). Morphine with topical LA was more effective than LA alone for central venous line placement in ventilated neonates (50,51). In addition, low-dose remifentanil combined with sucrose reduced the pain of insertion of central venous catheters (36).

HPBS pain can be reduced with procedure modification such as using an automated spring-loaded device, avoiding squeezing the heel, and using a wider area of the plantar surface of the heel (48,49,54–56).

Analgesia Table 4.2.1a
Blood sampling and peripheral cannulation in the neonate

		Direct evidence	Indirect evidence
Local anesthesia	Topical	1+	
Sucrose		1++	
Nonpharmacological		1+	
Procedure modifications		1+	

Analgesia Table 4.2.1b
Percutaneous central venous catheter insertion

		Direct evidence	Indirect evidence
Local anesthesia[a]	Topical	1+	
Opioids	Intravenous	1+	
Sucrose[a]		1+	1++

[a]Combined with Opioids.

4.2.2 Ocular examination for retinopathy of prematurity

Preterm infants 'at risk' of retinopathy of prematurity (ROP) should have regular ocular examination. An eyelid speculum is inserted to hold the eye open, and the retina is examined by indirect fundoscopy through a dilated pupil. In addition, a small proportion will require laser ablation of significant disease.

Recommendations

Sucrose may contribute to pain response reduction in examination for retinopathy: Grade A (57–60).

Infants undergoing examination for retinopathy should receive local anesthetic drops in combination with other measures if an eyelid speculum is used: Grade B (61–65).

Swaddling, developmental care, non-nutritive sucking, and pacifier should be considered for neonates undergoing examination for retinopathy: Grade B (57,60,63,66).

Laser treatment should be with general anesthesia if timely treatment is needed: Grade D (63).

Evidence

A combined analgesic approach using LA, a pacifier, swaddling, and the addition of a sweet solution is likely to be most effective for ROP screening examination pain (57,65). Oral sucrose prior to the screen reduced the behavioral pain scores in small groups of infants (59,60). Laser treatment is painful, and appropriate pain-relieving strategies should be employed (63). Laser treatment may be more rapidly available if sedation, analgesia, ventilation, and muscle relaxation are possible on the neonatal unit (63). See section 6.7 for further information on the use of sucrose.

Analgesia Table 4.2.2 Retinopathy of prematurity

		Direct evidence	Indirect evidence
Local anesthesia	Topical	1+	
Sucrose		1+	
Non-nutritive sucking		1+	
Comfort care package		1–	

4.2.3 Lumbar puncture (LP) in the neonate

Sampling of cerebrospinal fluid is often regarded as a minor procedure in infants; nevertheless, it is associated with pain that can be reduced by suitable analgesia (67).

Recommendation

Topical local anesthesia is effective in reducing lumbar puncture pain: Grade A (67,68).

Evidence

There have been few studies directly investigating LP pain in the neonate. Topical local anesthetic has been found to be effective (67). Indirect evidence suggests that subcutaneous infiltration of LA would also be effective, but it has not been 'consistently' shown to be superior to placebo in the neonate, in contrast to positive effects in older children and adults (69). A nomogram of weight to midspinal depth allows estimation of the depth of insertion of an LP needle (70,71). This has been correlated with

increased success rate (i.e., less red cell contamination).

Analgesia Table 4.2.3 Lumbar puncture in the neonate

		Direct evidence	Indirect evidence
Local anesthesia	Topical	1+	
	Infiltration[a]		1+
Sucrose			1++
Non-nutritive sucking			1+
Nonpharmacological			1+
Procedure Modification		2+	

[a]Older children and adults.

4.2.4 Urine sampling in the neonate

Urine sampling can be important to detect urinary tract infection in neonates and must be collected avoiding sample contamination. Direct catheterization of the urethra or catheterization of the bladder by the percutaneous suprapubic route is often preferred because some types of urine collection bags have a high rate of contamination, and 'clean catch' specimens can be difficult or time-consuming to collect.

Recommendations

Transurethral catheterization with local anesthetic gel is preferred as it is less painful than suprapubic catheterization with topical local anesthesia: Grade B (72,73).

Sucrose reduces the pain response to urethral catheterization: Grade C (74).

Evidence

Pain responses were observed in neonates and infants having either urethral or suprapubic catheterization with local anesthesia (72). Transurethral catheterization appeared to be less painful (72). Sucrose analgesia immediately before bladder catheterization in neonates and infants up to 3 months old was not effective at abolishing pain responses; however, a reduction in response was observed in the subgroup of those <30 days old (74). See section 6.8 for advice on the use and administration of sucrose.

Analgesia Table 4.2.4 Urine sampling in the neonate

		Direct evidence	Indirect evidence
Local anesthesia	Topical lubricant gel[a]		1+
Sucrose		1−	1++
Non-nutritive sucking			1+
Nonpharmacological			1+
Procedure modification[a]		1+	

[a]Urethral catheterization.

4.2.5 Chest drain (tube) insertion and removal

The management of this procedure in the neonate is discussed with that of older children in section 4.3.3.

4.2.6 Nasogastric tube placement

Nasogastric tube (NGT) insertion is a painful and distressing procedure frequently performed with little attention to pain-relieving strategies (75). Neonates who have not fully established enteral feeding or who have not developed a coordinated suck will require NGT feeds. In addition, the NGT is replaced to prevent nosocomial infection and when displaced. Passing a NGT is a skilled procedure, and in the UK, the Department of Health has published guidelines (CMO Update no.39, publ DoH, UK). In addition, the National Patient Safety Agency has recommended that only Medicina NGT is used to avoid erroneous intravenous drug delivery by the NGT route (NPSA/2007/19). See also sections 4.0, 4.1, and 4.2 for advice on the general management of painful procedures in neonates, infants, and children. The management of this procedure is also discussed with that of older children in section 4.3.5.

Recommendation

Sucrose can reduce the pain response from NGT insertion: Grade B (76).

Evidence

Sucrose (0.5 ml of 24%) given 2 min before NGT insertion reduced the behavioral pain score and physiological responses in a small number of stable preterm infants (76).

Analgesia Table 4.2.6 Nasogastric tube insertion

	Direct evidence	Indirect evidence
Sucrose	1+	1++
Non-nutritive sucking		1+
Nonpharmacological		1+

4.2.7 Immunization and intramuscular injection

The management of this procedure is also discussed with that of older children in section 4.3.6. There are two indications for IM injections: routine immunization and administration of vitamin K. In any other situation, an alternative route of administration should be used. The UK routine immunization schedule advises that vaccinations are given at 2, 3, and 4 months of age. A premature neonate born at <33 weeks of gestation is likely to receive these immunizations at the above ages on neonatal intensive care units.

Recommendation

Swaddling, breast-feeding or pacifier, and sucrose should be considered in neonates undergoing vaccination: Grade A (24,77,78).

4.3 Procedural pain management in infants and older children

Painful procedures are often identified as the most feared and distressing component of medical care for children and their families. See also general consideration for the management of procedural pain at the start of section 4.0, and section 4.1 for the management of procedural pain in the neonate. When managing procedural pain in infants, older children, and adolescents, special emphasis should be given not only to proven analgesic strategies but also to reduction in anticipatory and procedural anxiety by suitable preparatory measures. Families, play therapists, nursing staff, and other team members play key roles in reducing anxiety by suitable preparation. The personality, previous experience, and analgesic preferences of the child will influence management strategies. Analgesia/sedation with 50% nitrous oxide/oxygen by supervised self-administration should be considered where indicated, especially in children older than 6 years who can cooperate: see section 6.7. Sedation or general anesthesia may be needed for complex, invasive, or multiple procedures. See NICE Guideline CG112 'Sedation in Children and Young People' available at: http://www.nice.org.uk/CG112.

Good practice points

Children and their parents/carers benefit from psychological preparation prior to painful procedures.

Pain management for procedures should include both pharmacological and nonpharmacological strategies where possible.

50% nitrous oxide/oxygen should be considered for painful procedures in children who are able to cooperate with self-administration.

Sedation or general anesthesia should be considered, particularly for invasive, multiple, and repeated procedures.

4.3.1 Blood sampling and intravenous cannulation in children

For most children, venepuncture or intravenous cannulation may be a 'one-off' event, but children with chronic illness are likely to require multiple procedures, and this can be very distressing for the child, the family, and the medical team. When managing such pain in infants, older children, and adolescents, special emphasis should be given not only to proven analgesic strategies but also to reduction in anticipatory anxiety by suitable preparatory measures. Venepuncture or intravenous cannulation may be technically difficult – practitioners should not continue to try multiple cannulation sites unless the procedure is urgent or a more experienced practitioner is not available. In nonurgent cases, consider whether the test can be rescheduled, and enlist the help of a more experienced practitioner. See also section 4.0: general management of procedures, and 4.2: procedural pain in infants, older children, and adolescents.

Recommendations

Topical local anesthesia should be used for intravenous cannulation: Grade A (79–84).

Psychological strategies to reduce pain and anxiety should be used: Grade A (83,85,86).

Evidence

Topical LA, such as EMLA® or AMETOP® (amethocaine), has an established place in the management of venous cannulation with high-quality evidence for efficacy (79–82). Recent evidence suggests that amethocaine has an advantage over EMLA for cannulation (83,87). Amethocaine has a faster onset of action.

Newer preparations such as liposomal encapsulated LA or newer LA delivery systems may offer advantages in some situations. Buffered injected LA, for example, lidocaine + bicarbonate 10:1, administered with a fine 30-g needle subcutaneously prior to cannulation is faster in onset and may be as acceptable and effective as topical preparations (81,82,88).

Nitrous oxide (50–70%) inhalation has been used in children older than 6 years who can *self-administer* during venepuncture in some circumstances. 70% nitrous oxide is not routinely available for self-administration in the UK. 50% nitrous oxide and EMLA have been shown to be equally effective for venepuncture with further improvements in pain reduction using a combination of the two (79,89).

The efficacy of vapocoolant topical spray has not been clearly established. Vapocoolant spray was not effective in reducing pain in one study of intravenous cannulation but did show a modest reduction in pain in a later study (90,91). In a study of children's preferences, children who had experienced both methods selected both ethyl chloride and Ametop® equally (92). A combination of cooling and vibration (Buzzy®) with or without LA reduced pain and distress of venepuncture in one study (93).

Psychological approaches such as distraction should be offered to all children as it is easy to administer. Hypnosis can also be very effective for children requiring repeated interventions (83,86).

Analgesia Table 4.3.1
Blood sampling and IV cannulation in children

		Direct evidence
Local anesthesia	Topical	1++
	Infiltration	1++
50% nitrous oxide/oxygen		1+
Psychological preparation		1–
Psychological intervention		1++

4.3.2 Lumbar puncture in children

Lumbar puncture (LP) is necessary in acutely ill children in whom meningitis is suspected. These children are likely to be unwell and anxious, and they may also undergo other painful procedures such as venepuncture as part of diagnosis and treatment.

Other children require 'elective' or 'planned' LP: This may be for diagnostic reasons, such as evaluation of possible raised intracranial pressure, or for intrathecal treatments such as chemotherapy.

Positioning of the child is very important for success, and it is helpful to have assistance from trained staff with experience of correct positioning. Children who require multiple LPs may cope better with the addition of sedation (see NICE Guideline CG112 'Sedation in Children and Young People' available at: http://www.nice.org.uk/CG112) or general anesthesia.

See also section 4.0 and 4.2 on the general management of painful procedures.

Recommendations

Behavioral techniques of pain management should be used to reduce LP pain: Grade A (85,94).

Topical LA and LA infiltration are effective for LP pain and do not decrease success rates: Grade B (82,95,96).

50% nitrous oxide/oxygen should be offered to children willing and able to cooperate: Grade C (97).

Evidence

Few studies have directly examined the efficacy of analgesics in awake children undergoing lumbar puncture. Most commonly, local anesthesia is combined with sedative agents, such as midazolam, or biobehavioral techniques, such as distraction or other cognitive–behavioral interventions (85,94,95,98), is effective for LP pain, and may also be used in combination with LA (either topical or infiltration) and other strategies (97). Ketamine analgesia/sedation or general anesthesia is sometimes used in emergency departments and oncology units with appropriate facilities (99–101). However, recent studies indicate that analgesia practice for LP in emergency departments could be improved (102,103). It seems likely that older children, especially those who may only need to undergo this procedure once, may tolerate LP with appropriate behavioral techniques and local anesthesia, whereas children requiring multiple LPs should be offered sedation or GA (98).

There is some evidence that technique modification using pencil point needles instead of standard needles may reduce the incidence of post-LP headaches (104).

Analgesia Table 4.3.2 Lumbar puncture in children

		Direct evidence	Indirect evidence
Local anesthesia	Topical	1+	
	Infiltration	1–	
50% nitrous oxide/oxygen		2+	
Psychological interventions		1++	

4.3.3 Chest drain (tube) insertion and removal

Chest drains are necessary in children with pneumothorax, empyema, pleural effusions, following chest trauma and surgery. Pediatricians are most likely to need to insert chest drains in the Neonatal Intensive Care Unit to infants with pneumothorax. This procedure is becoming increasingly rare because of improvements in the management of Respiratory Distress Syndrome, e.g. the use of surfactant and ventilating infants at lower pressures. Older children require drains for management of empyema or for pneumothorax. Chest drains have become easier to insert recently with the development of small-bore Seldinger-type drains that reduce the need for blunt dissection of the chest wall: They are available for both neonates and older children.

Sedation (see NICE Guideline CG112 'Sedation in Children and Young People' available at: http://www.nice.org.uk/CG112) or general anesthesia should be considered for chest drain insertion; however, in an emergency, some children may tolerate this procedure using infiltration of buffered LA.

Studies agree that chest drain *removal* also causes significant pain. No single analgesic strategy has been shown to satisfactorily alleviate this pain in children, and it is likely that the optimum effects will be achieved using a combination of strategies.

See also section 4.0 and 4.2 for advice on the general management of painful procedures.

Good practice points

For chest drain insertion, consider general anesthesia or sedation combined with subcutaneous infiltration of buffered lidocaine. Selection of appropriate drain type may reduce pain by facilitating easy insertion.

For chest drain removal, consider a combination of two or more strategies known to be effective for painful procedures such as psychological interventions, sucrose or pacifier (in neonates), opioids, nitrous oxide, and NSAIDs.[1]

Evidence

There is little published evidence looking at analgesic options for chest drain insertion or removal. Chest drain insertion may require general anesthesia or sedation in combination with LA infiltration. Analgesia for removal of chest drains has included IV opioid, local anesthetics, and NSAIDs, but despite the use of these analgesics, significant pain is still reported (106,107). Inhalation agents such as nitrous oxide or isoflurane may have a role in these procedures, but further study is needed (108,109). *N.B. Nitrous oxide is contraindicated in the presence of pneumothorax*. Multimodal therapy, for example, IV morphine, nitrous oxide, topical LA, and NSAID, is likely to be superior to a single agent, but such combinations, although in clinical use, have not been studied.

Analgesia Table 4.3.3 Chest drain insertion and removal

	Direct evidence	Indirect evidence
LA: buffered lidocaine infiltration (insertion)		1++
LA: topicala (removal)		1+
Opioids[a] (removal)		1+
NSAIDS[a] (removal)		1+
50% nitrous oxide[a,b] (removal)	1–	
Psychological interventions		1++
Procedure modification (insertion)	3	

[a]May reduce but not abolish pain of chest drain removal.
[b]Contraindicated in the presence of pneumothorax.

4.3.4 Bladder catheterization and related urine sampling procedures

Urine specimens are usually obtained by 'clean catch' or midstream specimen (MSU). Urine may be obtained from young infants by means of suprapubic aspirate (SPA). Sampling by urethral catheterization appears to be less painful than SPA (72,110). Bladder catheterization may be required for radiological or other investigation of the renal tract, for example, micturating cystourethrogram (MCUG) also known as voiding cystourethrogram (VCUG). Consider whether MCUG is really necessary – it is a distressing procedure for the child and other less invasive techniques, such as dynamic renal scanning may provide the same information.

Bladder catheterization may also be required in children who develop urinary retention, particularly those receiving epidural analgesia postoperatively. Very ill patients in ICU may also require catheterization to monitor urine output. For children who are to receive postoperative epidural opioids after major surgery, consider 'prophylactic' bladder catheterization under general anesthesia at the time of surgery.

Sedation may also be indicated for some children; see NICE Guideline CG112 'Sedation in Children and Young People' available at http://www.nice.org.uk/CG112 for advice on sedation practice, and sections 4.0 and 4.2 on the general management of procedural pain.

[1]It is important to allow enough time for the chosen agent to reach their peak effect and to use adequate doses (105).

Good practice point

Lubricant containing local anesthesia should be applied to the urethral mucosa prior to bladder catheterization.

Recommendations

Psychological preparation and psychological and behavioral interventions should be used during bladder catheterization and invasive investigations of the renal tract: Grade B (111,112).

Infants: Consider procedure modification as urethral catheterization is less painful than SPA for urine sampling: Grade B (72,73).

Evidence

Bladder catheterization has been shown to cause significant pain and distress, but analgesia is not part of routine care in many institutions (113). More complex interventions, which include bladder catheterizations such as MCUG or VCUG, have also been shown to cause significant distress, which can be reduced by psychological preparation and behavioral pain management techniques such as distraction or hypnosis (111,112,114). Local anesthetics incorporated into lubricant gels are frequently used in adults to reduce the pain and discomfort of catheterization, but this has not been well studied in children. Pretreatment of the urethra with lidocaine 10 min before catheterization reduced pain in a group of children (16 girls, four boys) with a mean age of 7.7 years (115). However, in younger children (mean age 2 years), application of lidocaine gel to the 'genital mucosa' for only 2–3 min before the procedure and its subsequent use as a lubricant did not decrease pain (113). Techniques combining adequate preparation, local anesthesia, and behavioral interventions are likely to be more effective (116).

Analgesia Table 4.3.4
Bladder catheterization and urine sampling in children

		Direct evidence	Indirect evidence
Local anesthesia	Topical gel[a]	1+	
50% nitrous oxide			1+
Psychological preparation		1+	
Psychological intervention		1+	
Procedure modification[b]		1+	

[a]Applied 10 min before catheterization.
[b]Urethral catheterization instead of SPA.

4.3.5 Nasogastric tube insertion

See also sections 4.1, 4.2 and 4.3 for advice on the general management of painful procedures in neonates, infants, and children and 4.2.7 for NGT insertion in neonates. NGT insertion is a painful and distressing procedure frequently performed with little attention to pain-relieving strategies (75). Infants who are unwell and unable to feed, particularly those with respiratory problems such as bronchiolitis, may need to be 'tube fed' for a short period. NGT is often maintained in the postoperative period and may need to be re-inserted if they become displaced. Older children may also be fed via NGT, for example, in patients with cystic fibrosis who sometimes require supplementary feeding on multiple occasions. Clearly, it is particularly important to optimize pain management in those patients who are likely to need repeated NGT placement.

Passing a NGT is a skilled procedure, and in the UK, the Department of Health has published guidelines (CMO Update no.39, publ DoH, UK; NPSA/2007/19), which should be followed.

Good practice point

Topical local anesthetics such as lubricant gel containing lidocaine, applied prior to placement, are likely to reduce the pain and discomfort of NGT insertion.

Evidence

NGT insertion has been little studied in children. In the adult, topical local anesthesia and lubricants have been shown to reduce pain and facilitate placement (117–119). 10% nebulized lidocaine is also effective in adults but may also slightly increase the incidence of epistaxis (120). A recent RCT did not find any benefit from nebulized lidocaine in children between 1 and 5 years (121). The additional use of vasoconstrictors such as topical phenylephrine or cocaine may reduce this risk, findings that have not been confirmed in children. Indirect evidence also suggests that the use of psychological/behavioral techniques may be of benefit in older children.

Analgesia Table 4.3.5 Nasogastric tube insertion

	Direct evidence	Indirect evidence
Topical LA		1++
Non-nutritive sucking[a]		1+
Tactile stimulation[a]		1+
Psychological preparation		1+
Psychological intervention		1+

[a]Infants.

4.3.6 Immunization and intramuscular injection

Immunization schedules result in increasing numbers of intramuscular injections being administered to infants and children. At 2 and 3 months, infants are offered diphtheria, tetanus, pertussis, hemophilus (Hib), and polio immunization as one vaccination, with a separate meningococcal or pneumococcal vaccine. All 3 are given at 4 months. Children receive further immunizations at 1 year and 15 months, again at preschool, and finally at school leaving. Intramuscular administration of asparaginase to children with leukemia, and long-acting penicillin therapy are other examples. The pain of these injections is widely acknowledged and contributes to anxiety in patients and their parents/carers, particularly regarding vaccinations. There is now evidence that such pain may be reduced by a number of strategies. Knowledge that practitioners have considered the use of these strategies may help parents in their decisions about immunization. It is important that treatable pain is not a barrier to the childhood immunization program.

See also sections 4.0, 4.1, and 4.2 on the general management of procedural pain.

Good practice point

Intramuscular injections should be avoided in children as part of routine care. If intramuscular injection is unavoidable, pharmacological and nonpharmacological strategies should be employed to reduce pain.

Recommendations

Psychological strategies such as distraction should be used for infants and children undergoing vaccination: Grade A (85,122–124).

Consider additional procedure modifications such as vaccine formulation, order of vaccines (least painful first) needle size, depth of injection (25 mm 25 gauge needle), or the use of vapocoolant spay: Grade A (125–132).

Swaddling, breast-feeding or pacifier, and sucrose should be considered in infants undergoing vaccination: Grade A (7,78,133,134).

Evidence

There are two phases of immunization pain: the initial pain of the needle piercing the skin and injection of a volume of vaccine into the muscle or subcutaneous tissue, followed by a later phase of soreness and swelling at the vaccination site because of subsequent inflammatory reaction. Studies have generally investigated strategies designed to deal with the former, presumably because this is perceived to be the most unpleasant component. Children typically dread needle-related pain; the use of either nonpharmacological or pharmacological pain reduction strategies may reduce subsequent negative recall (123). There is good evidence that nonpharmacological methods, particularly distraction, can reduce immunization pain (85,122,123,135). There is also evidence of benefit from nonpharmacological strategies in neonates and young infants < 2 months including swaddling, non-nutritive sucking, and sucrose and glucose (7,133,134,136). The optimal dose of sucrose has not yet been determined, and its effectiveness in infants from 1 month is uncertain (137). See section 6.7 for information on the use of sucrose.

Procedure modifications may alter pain responses. Some combined vaccine formulations (MMR-Priorix, lower dose DTP vaccine booster Tdap) appear to be less painful, and this requires further study (127,129,138). Longer (25 mm) needles and deeper intramuscular rather than subcutaneous injection can reduce local reactivity following immunization (126,130). Swab-applied vapocoolant (Fluori-methane) was as effective as topical analgesia when both were combined with distraction (125). Simultaneous, rather than sequential injection of multiple vaccines was less painful in one study (139).

Topical local anesthesia (EMLA®, Ametop®) is clearly capable of reducing components of vaccination pain in both infants and older children, but the efficacy and the balance of effectiveness against cost are difficult to determine from the studies presently available (7,140–143). Lidocaine local anesthesia added to asparaginase or benzyl penicillin injection reduced the pain response in two studies; again, this approach requires further investigation (144,145).

Analgesia Table 4.3.6 Immunization and intramuscular injection

		Direct evidence	Indirect evidence
Local anesthesia	Topical	1+	
Sucrose		1–	
Psychological interventions		1++	
Psychological preparation			1+
Procedure modifications		1+	

4.3.7 Repair of lacerations in children

Traumatic lacerations of the skin and scalp are common presentations in the emergency department. Acceptable, safe, and effective repair is often a considerable challenge. For minor lacerations without general anesthesia or sedation, a combination of pharmacological and nonpharmacological techniques is likely to be

most effective. There are a number of less painful alternatives to simple wound suture in the awake patient: Tissue adhesives in simple low-tension wounds and the hair apposition technique (HAT) in scalp lacerations are examples.

Also see section 4.0 and 4.2 for general considerations in procedural pain management.

Good practice point

For extensive wounds or children who are very anxious consider sedation or general anesthesia.

Recommendations

For repair of simple low-tension lacerations, tissue adhesives should be considered as they are less painful, quick to use, and have a similar cosmetic outcome to sutures or adhesive skin closures (steri-strips): Grade A (146–148).

Topical anesthetic preparations, for example, LAT (lidocaine–adrenaline–tetracaine) if available, can be used in preference to injected LA, as they are less painful to apply; it is not necessary to use a preparation containing cocaine: Grade A (149–153).

Buffering injected lidocaine with sodium bicarbonate should be considered: Grade A (88).

'HAT' should be considered for scalp lacerations. It is less painful than suturing, does not require shaving, and produces a similar outcome: Grade B (154).

If injected lidocaine is used, pretreatment of the wound with a topical anesthetic preparation, for example, lidocaine–adrenaline–tetracaine (LAT) gel, reduces the pain of subsequent injection: Grade B (155,156).

50% nitrous oxide reduces pain and anxiety during laceration repair: Grade B (157–159).

Evidence

Laceration repair has been relatively well studied in children. There are a number of alternatives to simple wound suture in the awake patient. Tissue adhesives in simple low-tension wounds and the hair apposition technique (HAT) in scalp lacerations are less painful alternatives (147,154). A number of topical local anesthetic mixtures are available; they can give equivalent analgesia to infiltrated local anesthetic and are less painful to apply although a recent systematic review in adults and children concluded that there was insufficient evidence to unreservedly recommend topical LA in preference to injected LA (82,153). A systematic review including trials in adults and children found that 'buffering' local anesthetics with sodium bicarbonate significantly reduces the pain of injection (88). Nitrous oxide has been shown to be effective in reducing pain, anxiety, and distress in cooperative children (157,158). See section 6.7 for information on the use of nitrous oxide. Psychological techniques such as distraction and relaxation are also likely to be useful (85).

Analgesia Table 4.3.7 Repair of lacerations in children

		Direct evidence	Indirect evidence
Local anesthesia	Topical	1++	
	Infiltration	1++	
	Buffered infiltration	1++	
50% nitrous oxide		1+	
Procedure modification		1++	
Psychological intervention			1++

4.3.8 Dressing changes in the burned child

Children with burns often require repeated, often extremely painful, dressing changes. Children with severe burns are normally cared for in a specialist unit, but some children will be seen in Emergency Departments. Initial dressing changes are likely to be performed under general anesthesia, and if children remain very distressed, this option may be favored for subsequent procedures. Sedation is sometimes used to supplement analgesia for burns dressings, see NICE Guideline CG112 'Sedation in Children and Young People' available at: http://www.nice.org.uk/CG112. In the early stages of burn pain management, children may require continuous infusion of potent opioids such as morphine, and additional analgesia will be required prior to dressing changes (160).

Both pharmacological and nonpharmacological techniques should be used in the management of painful dressing changes, see section 4.0, 4.1, and 4.2 for advice on the general management of painful procedures.

Recommendations

Potent opioid analgesia given by oral, transmucosal, or nasal routes according to patient preference and availability of suitable preparations should be considered for dressing changes in burned children: Grade A (161–164).

Nonpharmacological therapies such as distraction and relaxation should be considered as part of pain management for dressing changes in burned children: Grade B (165–170).

Evidence

The evidence base for managing burn pain in children is small and incomplete. Opioids are used extensively and should be given as necessary by intravenous or other routes (160). There are a number of small studies comparing different opioid formulations and routes of administration, such as transmucosal or intranasal fentanyl, hydromorphone, oxycodone and morphine by the oral route (161–164).

There is evidence for distraction with children using a variety of devices – such as helmet Visual Reality devices or hand-held multimodal devices where the child is an active participant in the game they are playing being more effective than standard distraction when burns dressings are being changed (168–173).

Small studies have investigated different creams or dressings with some being less painful – more research is needed in this area (174–176). Nitrous oxide is used extensively for single painful procedure in children who are able to cooperate; multiple or frequent administration may lead to bone marrow toxicity. Nitrous oxide has not been directly studied in this patient group, although there is one small cohort study assessing parent and patient satisfaction (177). See section 6.7 for more information on the use of nitrous oxide.

Analgesia Table 4.3.8 Dressing changes in burned child

	Direct evidence	Indirect evidence
Opioids	1++	
Nitrous oxide[a]		1++
Psychological preparation		1+
Psychological intervention	1+	

[a]No data for multiple administrations.

4.3.9 Botulinum injections for children with muscle spasm

Botulinum toxin is used to relieve muscle spasm; in pediatric practice, this is most often the spasticity associated with cerebral palsy. These injections can take a long time – usually, multiple sites are chosen, and there are three phases to the procedure: initial puncture, localization of correct muscle point, and then injection. There is very little evidence for pain management strategies: In practice, many children are likely to be offered general anesthesia or sedation.

One observational study was identified, which investigated the level of pain felt by children undergoing this procedure with local anesthetic cream and 50% nitrous oxide. In this study, half the children experienced severe pain, but the rest of the children managed well with this combination (178). Further research is needed.

Good practice point

50% nitrous oxide/oxygen should be considered in children who are able to cooperate with self-administration.

Analgesia Table 4.3.9 Botulinum toxin injections

	Direct evidence	Indirect evidence
50% nitrous oxide		1+
Topical LA		1+
Psychological preparation		1+
Psychological intervention		1+

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Section 5.0
Postoperative pain

Contents

5.1 General principles of postoperative pain management

Good practice points

Providers of postoperative care should understand the general principles of good pain management in children; this includes knowledge of assessment techniques and the use of analgesics at different developmental ages.

Pediatric anesthetists are responsible for initiating postoperative analgesia. They should liaise with patients and their families/carers, surgeons, and other members of the team providing postoperative care to ensure that pain is assessed and suitable ongoing analgesia is administered.

Postoperative analgesia should be appropriate to developmental age, surgical procedure, and clinical setting to provide safe, sufficiently potent, and flexible pain relief with a low incidence of side effects.

Combinations of analgesics should be used unless there are specific contra-indications, for example; local anesthetics, opioids, NSAIDs, and paracetamol can be given in conjunction, not exceeding maximum recommended doses.

Introduction

Postoperative care is frequently shared between heath professionals from different disciplines: they should be suitably qualified, including an awareness of the general principles of pain assessment and pain management in children. Postoperative analgesia should be planned and organised *prior to surgery* in consultation with patients and their families or carers, and other members of the perioperative team. The pediatric anesthetist is responsible for initiating suitable postoperative analgesia; this should be considered to be part of the overall plan of anesthesia.

Analgesia is an integral part of surgical anesthesia, and therefore, potent analgesics are administered during general anesthesia in the form of opioids, local anesthetics, and other drugs. Patients and carers should be made aware that the effects of these analgesics will wear off in the postoperative period, leading to an increase in pain and the need for further analgesia. Patients should not be discharged from the Postoperative Care Unit (postanesthesia recovery area) until satisfactory pain control is established and ongoing analgesia is available.

Prior to discharge from the hospital, patients and their families should be given clearly presented information and advice regarding the assessment of pain and the administration of analgesia at home. It is also

necessary to ensure that the patient will have access to suitable analgesia.

Pain after surgery is usually most severe in the first 24–72 h but may persist for several days or weeks. Analgesia can be given regularly (by the clock) in the early postoperative period and then 'as required' according to assessed pain. Drugs to counteract unwanted effects of analgesia or other side effects of surgery such as PONV should also be available and administered when necessary.

Postoperative pain should be assessed frequently: see section 3.0 for further information. Analgesic regimens should be sufficiently flexible to allow for inter-individual differences in the response to analgesics and the variation in the requirement for pain relief that occurs during the postoperative period.

5.2 ENT surgery

5.2.1 Myringotomy

Drainage of the middle ear, usually with insertion of a tube, is a treatment for otitis media. Myringotomy is usually considered to be a minor procedure, undertaken on a day-case basis. See also section 5.1 for the general principles of postoperative pain management.

Good practice point

As myringotomy is a brief procedure, oral paracetamol or NSAID should be administered preoperatively to ensure adequate analgesia at the end of surgery.

Recommendations

Oral paracetamol or NSAIDS (ibuprofen, diclofenac, or ketorolac) in suitable doses can achieve adequate early postoperative analgesia: Grade B (1–4).

Opioids are effective but not recommended for routine use because of side effects: Grade B (1,5–8).

Evidence

Paracetamol (oral) produces dose-related analgesia; 10 $mg \cdot kg^{-1}$ is no better than placebo (3) or is associated with higher supplemental requirements (8), whereas pain scores are lower with 15–20 $mg \cdot kg^{-1}$ (1,2,4,5,9).

Ibuprofen and diclofenac appear to provide similar analgesia to paracetamol (2,10), but the combination has not been tested.

Ketorolac 1 $mg \cdot kg^{-1}$ (intravenous) provides minor improvements in analgesia when compared with low doses of paracetamol, 10 $mg \cdot kg^{-1}$ (3,8); paracetamol 10 $mg \cdot kg^{-1}$ + codeine 1 $mg \cdot kg^{-1}$ (8); paracetamol 15 $mg \cdot kg^{-1}$ (but only first 10 min there was no difference at 20 min) (4). See section 6.5 for recommended doses of ketorolac and other NSAIDS.

Opioids, for example codeine, butorphanol, or fentanyl, have been associated with increased side effects when compared with NSAIDs or paracetamol, without clinically significant improvements in analgesia; therefore, their use is not warranted for routine myringotomy:

i. increased sedation and time to discharge for oral codeine: (1), nasal fentanyl (7) and nasal butorphanol (6)

ii. increased vomiting with oral codeine or nasal butorphanol (8).

LA block of the auricular branch of the vagus provided equivalent analgesia to intranasal fentanyl (11).

Analgesia Table 5.2.1

	Direct evidence
Opioid[a]	1–
NSAID	1–
Paracetamol	1–

[a]Not routinely recommended because of side effects: see text.

5.2.2 Tonsillectomy

Tonsillectomy (±adenoidectomy) is one of the most frequently performed procedures in children. Chronic or recurrent tonsillitis with tonsillar hyperplasia leading to upper airway obstruction, for example in sleep apnea syndromes, is the most frequent indication for tonsillectomy. The choice of analgesia, postoperative monitoring, and duration of hospital admission is influenced by the potential for serious complications such as apnea, perioperative bleeding, and postoperative nausea and vomiting (PONV). Pain after tonsillectomy can persist for many days. See also section 5.1 for the general management of postoperative pain.

Good practice point

As significant levels of pain, behavioral disturbance, sleep disruption, and altered activity can persist for 5–8 days following tonsillectomy, regular administration of analgesia may be necessary during this period. Information for families about pain assessment and medication use following discharge is particularly important.

Recommendations

A combination of individually titrated intraoperative opioids, dexamethasone, and regularly administered perioperative mild analgesics (NSAIDS and/or paracetamol) is recommended for management of tonsillectomy pain: Grade A (12,13).

Topical application or injection of local anesthetic in the tonsillar fossa improves early pain scores following tonsillectomy: Grade A (14,15).

Tramadol can produce similar analgesia to morphine or pethidine: Grade B (16–18).

Peritonsillar injection of tramadol has no advantage over systemic administration: Grade B (19,20).

Intraoperative intravenous ketamine does not provide significant postoperative advantage compared with opioid: Grade B (16,17,21,22).

Implementation of standardised protocols including intraoperative opioid ± anti-emetic, perioperative NSAID (diclofenac or ibuprofen), and paracetamol is associated with acceptable pain relief and low rates of PONV: Grade C (23,24).

Evidence

Significant levels of pain, behavioral disturbance, sleep disruption, and altered activity can persist for 5–8 days following tonsillectomy (25–28). Regular administration of paracetamol and NSAID is necessary for several days postoperatively, and adequate parental education about pain assessment and medication use is required.

Opioids: Intraoperative opioids are given during tonsillectomy and may be required in the postoperative period (12). Morphine is the prototype opioid, but there has been some interest in the use of tramadol following tonsillectomy.

Tramadol produces similar analgesia and side effects to morphine (29) and pethidine (16). Tramadol 1 $mg{\cdot}kg^{-1}$ was equianalgesic with IV paracetamol 15 $mg{\cdot}kg^{-1}$ in one study (30). One study reported less nausea with tramadol than morphine (18). In patients with sleep apnea tramadol was associated with fewer episodes of oxygen desaturation at one time point postoperatively (1–2 h, no difference at earlier or later time points to 6 h) (29). Comparison of intravenous and peritonsillar injection of tramadol 2 $mg{\cdot}kg^{-1}$ reported minor improvements with peritonsillar injection (19), but effects are likely to be related to systemic absorption. Tramadol 1 $mg{\cdot}kg^{-1}$ (IV), 2 $mg{\cdot}kg^{-1}$ (IM), or 3 $mg{\cdot}kg^{-1}$ by peri-tonsillar injection reduced pain scores when compared with placebo (20,31). Of particular concern, children in these placebo groups received no intra-operative analgesia. However, tramadol was less effective than ketoprofen (higher pain scores and higher postoperative PCA fentanyl) and did not differ from placebo in one study (32).

NSAIDS improve analgesia when compared with placebo (10/11 studies) and provide similar analgesia to opioids (7/8 studies) and paracetamol (3/3 studies) (33). A systematic review found that heterogeneity of the data precluded meta-analysis, and many studies comparing two active treatments were not sensitive enough to show a difference (12). Subsequent studies have reported similar analgesia with ketorolac and fentanyl (34), no improvement with addition of rofecoxib to opioid and paracetamol (35), and no difference in pain scores but increased rescue analgesic requirements with IV paracetamol compared with pethidine (36). Ketoprofen improved analgesia in the first 6 h postoperatively in comparison with tramadol or placebo (32).

Paracetamol is more effective given orally prior to surgery than rectally after induction of anesthesia, it reduces opioid requirements and PONV (37–39).

Local anesthesia: Two recent meta-analyses reported statistically significant reductions in postoperative pain scores with local anesthetic techniques for up to 48 h, but the effect size decreased after the first 4–6 h (14,15). Topical application and infiltration were equally effective (14), and no difference was found between LA infiltration before or after removal of the tonsils (15). Postoperative analgesic requirements were reduced (15), but there was no significant difference in adverse events (14) or PONV (15). In additional studies, bupivacaine infiltration and topical levobupivacaine swabs improved pain scores but did not alter PONV (40,41). Others reported no benefit with peritonsillar LA infiltration (42) and similar analgesia when topical 2% viscous lignocane was compared with rectal diclofenac (43).

Ketamine (IV) improves analgesia when compared with placebo (21,44,45) but provides no advantage when compared with equianalgesic opioid (17,46) and may increase side effects (22). Addition of ketamine 0.25 $mg{\cdot}kg^{-1}$ to morphine 0.1 $mg{\cdot}kg^{-1}$ did not significantly improve analgesia (47). Topical application on swabs (ketamine 20 mg in children aged 3–12 years) (48) or peritonsillar infiltration reduced very early pain scores and opioid requirements (49), effects may relate to systemic absorption. The combination of ketamine 0.5 $mg{\cdot}kg^{-1}$ IV and topical bupivacaine infiltration resulted in minor reductions in pain scores

when compared with LA alone and saline control groups (41).

Dexmedetomidine (IV) may reduce opioid requirements and respiratory side effects in children after tonsillectomy, this may particularly benefit those with obstructive sleep apnea (OSA) or respiratory compromise. One microgram per kilogram produced less respiratory depression than 100 $\mu g \cdot kg^{-1}$ morphine but less effective analgesia (50). Higher doses, 2 and 4 $\mu g \cdot kg^{-1}$, lengthened time to rescue opioid analgesia but increased sedation in the early postoperative period when compared to fentanyl 1 or 2 $\mu g \cdot kg^{-1}$ IV (51). Dexmedetomidine 2 $\mu g \cdot kg^{-1}$ + 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ intraoperative reduced early postoperative opioid requirements and agitation in children with OSA compared with fentanyl 1 $\mu g \cdot kg^{-1}$ (52).

Dexamethasone reduces PONV and postoperative pain scores following tonsillectomy (13,53).

Most meta-analyses of posttonsillectomy analgesia have focused on PONV and bleeding rather than analgesic efficacy. PONV following tonsillectomy is reduced by NSAID presumably because of a reduction in opioid requirement (33,54), and by intraoperative dexamethasone (see above). As posttonsillectomy bleeding is relatively rare, meta-analyses have included different trials and reached different conclusions:

- Bleeding is increased by aspirin but not ibuprofen or diclofenac (seven trials) (55).
- Risk of bleeding and reoperation increased (NNH 29), and NSAIDS should not be used (seven trials) (56).
- Risk of reoperation (NNH 60) but not bleeding increased, and NSAIDS should be used cautiously (25 trials) (33)
- NSAIDS do not increase risk of bleeding or reoperation but further studies required (13 pediatric trials) (54).

Although meta-analyses are currently inconclusive, perioperative diclofenac and ibuprofen appear to be associated with minimal risk of posttonsillectomy bleeding. Early studies using high doses of ketorolac have been included in the meta-analyses, but there are insufficient data to assess the risks associated with different NSAIDS.

Analgesia Table 5.2.2

Agent	Technique	Direct evidence
LA[a]	Tonsillar fossa injection	1+*
	Topical	1+*
Opioid		1+
	Tramadol	1+
Dexamethasone		1+
Ketamine		1+
NSAIDS		1+
Paracetamol		1+

[a]No differences have been demonstrated based on route (topical vs infiltration), type of LA, or time of injection (pre- vs post-removal).

5.2.3 Mastoid and middle ear surgery

Mastoidectomy may be performed to remove infected tissue or cholesteatoma. As the incidence of chronic suppurative otitis media is declining in many populations, this surgery is now less frequently required in the UK. Middle ear surgery, such as reconstruction of a damaged tympanic membrane by placement of surgical grafts, may be associated with significant PONV. See also section 5.1 for the general management of postoperative pain.

Recommendations

Great auricular nerve block can provide similar analgesia and reduced PONV compared with morphine. Preincision timing of the block confers no additional benefit: Grade B (57,58).

Evidence

There are relatively few controlled trials specifically investigating pain during and after mastoidectomy and invasive middle ear surgery, and no further studies since the last edition of this guideline. As NSAIDS and paracetamol improve analgesia for middle ear procedures, there is indirect evidence that they provide beneficial supplemental analgesia for mastoid surgery. However, compared with middle ear surgery, mastoid surgery is associated with increased pain: patients are therefore more likely to require opioids, treatment for PONV and hospital admission (59). In procedures that require a postauricular incision, LA block of the great auricular nerve can provide similar analgesia and reduced PONV compared with morphine (57). No difference was found between performing the block preincision vs prior to the end of surgery (58).

Analgesia Table 5.2.3

Agent	Technique	Direct evidence	Indirect evidence
LA	Greater auricular nerve block	1–	
Opioid		1–	
NSAID			1–
Paracetamol			1–

5.3 Opthalmology

5.3.1 Strabismus surgery

Strabismus surgery (correction of squint) is associated with a high incidence of PONV, and intraoperative tension on ocular muscles may provoke a vagal response (oculocardiac reflex). See also section 5.1 for the general management of postoperative pain.

Recommendations

Intraoperative LA blocks (subtenon's or peribulbar) reduce PONV and may improve perioperative analgesia in comparison with IV opioid but provide no benefit over topical LA: Grade B (60–64).

Topical NSAIDS do not improve pain scores or postoperative analgesic requirements when compared with topical LA or placebo: Grade B (65–67).

Intraoperative opioid and NSAID provide similar postoperative analgesia, but opioid use is associated with increased PONV: Grade B (68–71).

Evidence

In many trials, reduction of PONV rather than improvement in analgesia has been the primary outcome. The duration of surgery varies from 25 to 80 min in the reported studies, and many do not discriminate between unilateral or bilateral surgery or procedures involving single or multiple muscles. This may contribute to the variability across studies in the incidence of side effects and analgesic requirements.

Peribulbar or subtenon's LA blocks reduce intraoperative oculocardiac reflex responses (60,62,63) and PONV (60,62,63) when compared with intraoperative opioid. Peribulbar or subtenon blocks reduce perioperative analgesic requirements when compared with opioid in some (60,63) but not all (61,62) trials. No complications of LA injections were reported in these studies, but patient numbers are small. Sub-tenon's block provided no benefit compared with less invasive topical tetracaine application (64). Topical LA applied prior to and at the completion of surgery reduced early distress (first 30 min) but did not influence pain at later time points or reduce supplemental analgesic requirements (72).

No difference in postoperative pain scores or analgesic requirement has been detected between topical LA drops and topical NSAIDS (65,67). Pain scores (CHEOPS) were not reduced by topical NSAIDS when compared with placebo (66,67), but the authors questioned the sensitivity of this measure for ocular pain.

Direct comparisons of intraoperative NSAID and opioid (PR diclofenac vs IV morphine) (71) (IV ketorolac vs IV pethidine) (70) (IV ketorolac vs IV fentanyl) (68) have reported no difference in postoperative pain scores or supplemental analgesic requirements but increases in PONV in patients given opioids. Comparison of intraoperative remifentanil and fentanyl reported higher early pain scores but less PONV with remifentanil (73). Comparisons of NSAID and placebo have shown minor improvements in pain score and reductions in supplemental analgesic requirements (69,74).

Analgesia Table 5.3.1

Agent	Technique	Direct evidence	Indirect evidence
LA	Subtenon block[a]	1–	
LA	Peribulbar[a]	1–	
LA	Topical[a]	1+	
Opioid	Parenteral[b]	1–	
NSAID	Topical	1–	
	Systemic[b]	1–	
Paracetamol			1–

[a]Few comparisons, but no advantage of subtenon over topical in one trial.
[b]Similar analgesia with systemic NSAID and opioid but increased PONV with opioid; oral or rectal paracetamol given as part of multimodal analgesia to all patients in several trials but efficacy not directly compared with other agents.

5.3.2 Vitreoretinal surgery

Vitreoretinal and retinal detachment surgery are associated with significant postoperative pain and PONV. Supplemental local anesthetic techniques may have a role, but the relative benefit vs risk has not been fully evaluated. See also section 5.1 for the general management of postoperative pain.

Recommendations

In vitreoretinal surgery, NSAID can provide similar analgesia but lower rates of PONV compared with opioid: Grade C (75).

Peribulbar block improves early analgesia and may reduce PONV compared with opioid: Grade C (60,76–78).

Evidence

Ketoprofen and pethidine provided similar levels of analgesia, but PONV was less with ketoprofen (75).

Peribulbar LA block appears to be effective (60,76). Concerns have been expressed that peribulbar block may present a higher risk in children than subtenon's block as the eye occupies a relatively greater volume of the bony orbit in a child, and large volumes of LA have been used in trials of peribulbar block (79). Compared with fentanyl, subtenon's LA block reduces the incidence of intra-operative oculo-cardiac reflexes and improves early analgesia (77,80), but only one trial showed a reduction in analgesic requirements and PONV (77). There has been no evaluation of the risk vs benefit of these procedures in children.

Topical LA gel at the beginning of surgery reduced intra-operative, but not postoperative, analgesic requirements (81).

Analgesia Table 5.3.2

Agent	Technique	Direct evidence	Indirect evidence
LA	Peribulbar block[a]	2+	
	Subtenon block	1–	
Opioid		1–	
NSAID		1–	
Paracetamol			1–

[a]No analysis of risk–benefit for peribulbar block.

5.4 Dental procedures

Dental procedures in children may range from minor restoration and conservation requiring little or no postoperative analgesia, to variable numbers of extractions, and sometimes more extensive surgery leading to significant postoperative pain. See also section 5.1 for the general management of postoperative pain.

Recommendations

NSAIDS with or without paracetamol reduce pain following dental extractions: Grade B (82–84).

Swabs soaked with bupivacaine on exposed tooth sockets following extraction produce no or minor improvements in pain in the immediate postoperative period: Grade B (85,86).

Intraoperative LA infiltration reduces postoperative pain following dental extractions, but provides little additional benefit over NSAIDS and paracetamol alone: Grade B (83,84,87,88).

Evidence

The degree of postoperative pain following dental extractions increases with the number of teeth removed (89,90).

NSAIDS (82,91,92) and combinations of NSAID and paracetamol (83,84,88) reduce pain following dental extractions. However, adding paracetamol to ibuprofen did not improve early analgesia (15 min postoperatively) compared with ibuprofen alone in one study (82).

Opioids: no differences in analgesia were shown in comparisons with NSAIDS for extractions (93,94), but opioids may produce increased PONV (94). Similarly, for dental restorations without extractions, paracetamol provided adequate analgesia, pain scores were slightly lower with pethidine, but sedation was increased (95).

LA infiltration (2% lignocaine with adrenaline) added to NSAID ± paracetamol (83,84,88,92) provides little additional benefit following dental extractions, but less postoperative bleeding in the recovery room (reduced need for suctioning rather than quantified losses) was noted in one trial (88). Addition of morphine (25 $\mu g \cdot kg^{-1}$) to the local anesthetic injection did not improve analgesia (96). The soft tissue numbness associated with LA infiltration may produce distress and increase biting of lips and cheeks in young children (92). Distressing numbness was avoided by intraligamental injection of LA, but adding this to NSAID and paracetamol provided no additional benefit (83) or minor improvements in early analgesia (5 min) only (84). No improvements in analgesia or distress were found when bupivacaine-soaked swabs in the dental socket were added to paracetamol 15 $mg \cdot kg^{-1}$ (86) or diclofenac (85).

Analgesia Table 5.4

Agent	Technique	Direct Evidence
LA	Local infiltration[a]	1+
	Soaked swabs[a]	1–
Opioid		1–
NSAID		1+
Paracetamol		1–

[a]Improvements in early analgesia and no additional benefit over NSAID ± paracetamol.

5.5 General surgery and urology (minor and intermediate)

5.5.1 Sub-umbilical surgery

This category has been included because many studies have used a combination of different surgical procedures from the sub-umbilical area as the operative model, for example, repair of inguinal hernia, orchidopexy, orchidectomy, circumcision, phimosis, hypospadias, hydrocoele, vesico-ureteric reflux, testicular tortion, appendicectomy. Postoperative pain is unlikely to be equivalent following each of these different procedures (97), but they are not uniformly distributed between studies and the numbers of individual procedures in each study are often low, thereby making it impractical to look at each procedure in isolation. Refer to other pages in this section for more information on specific procedures, see also section 5.1 for the general management of postoperative pain.

Recommendation

LA should be used when feasible: wound infiltration, transversus abdominis plane (TAP) block, ilio-inguinal nerve block, and caudal analgesia are effective in the early postoperative period following sub-umbilical surgery: Grade A (98–103).

Evidence

The majority of studies compared differing drug combinations in central or peripheral nerve blockade. Caudal epidural neuraxial block was the most commonly studied technique and demonstrated good efficacy in all studies with a low failure and serious complication rate. This is in agreement with large case series of this technique (104–107). Efficacy was equivalent irrespective of the local anesthetic agent used, and there was little difference in the rate of side effects, caudal analgesia has been used with either general anesthesia or sedation for surgery (100,102,107–109). The optimal concentration and volume of LA has not been elucidated, but concentrations of levobupivacaine and ropivacaine below 0.2% have been associated with lower efficacy in some studies (110–112).

Caudal neuraxial analgesic additives[1]: with LA: the addition of caudal S-ketamine, neostigmine, clonidine, dexmedetomidine, midazolam, buprenorphine, fentanyl, and morphine increased analgesic efficacy and prolonged the duration of the block, with little reported increase in side effects in most studies (113–123). In contrast, other studies show that there is no benefit to adding midazolam, magnesium, or sufentanil to LA via the caudal route (124–126). Clonidine, S-ketamine, and buprenorphine were more effective when given by the caudal route compared with the intravenous route (115,120,127). In direct comparisons, either caudal clonidine or midazolam were better than morphine (113,128).

Without LA: a combination of S-ketamine and clonidine demonstrated better analgesic efficacy than S-ketamine alone via the caudal route (129). The use of such adjunctive analgesia requires further research to better identify safety profile, risk–benefit and dose; see also section 6.3 for a further discussion of neuraxial analgesia.

Ilio-inguinal nerve block was shown to be effective, but overall efficacy was generally lower than in studies of caudal block (98,130). The use of ultrasound to place the ilio-inguinal block improved the quality of the block, decreased supplementary opioid use, and decreased the amount of local anesthetic used (131). No benefit was seen from adding clonidine to the local anesthetic in ilio-inguinal nerve block (100,132).

TAP block is feasible with initial reports of good efficacy. An ultrasound-guided technique was shown to be effective in the intraoperative and early postoperative period, though efficacy was less when compared with ultrasound-guided ilio-inguinal nerve block for inguinal surgery (103).

LA wound infiltration/instillation is effective in the early postoperative period, it was equivalent to ilio-inguinal block with no further benefit from using them in combination in one study (98,101).

[1]Note on caudal additives: not all additives have undergone rigorous safety testing and concerns regarding potential toxic effects have been expressed. See Section 6. 3

Analgesia Table 5.5.1 Sub-umbilical Surgery

Agent	Technique	Direct evidence	Indirect evidence
LA	Wound infiltration[a]	1+	
LA	Ilio-inguinal nerve block[a]	1+	
LA	TAP Block	1−	
LA	Caudal epidural	1+	
LA + Ketamine[b]	Caudal epidural	1+	
LA + Clonidine[b]	Caudal epidural	1+	
Opioid[c]			1+
NSAID[c]			1+
Paracetamol[c]			1+

[a]Possibly lower efficacy than caudal block: more studies are required.
[b]Note on caudal additives: not all additives have undergone rigorous safety testing, and concerns regarding potential toxic effects have been expressed. See Section 6.
[c]As part of a multi-modal technique

5.5.2 Circumcision

Circumcision is regarded as a relatively minor surgical procedure, but it may be associated with significant postoperative pain and distress. It is usually undertaken on an out-patient or day-case basis. Circumcision in the neonate is considered separately in section 5.5.3. See sections 5.1 for the general management of postoperative pain and 5.5.1 for a discussion of sub-umbilical surgery.

Good practice point

Analgesia with opioid alone should be avoided if possible because of lower efficacy and higher incidence of side effects in comparison with LA techniques.

Recommendation

Caudal epidural and dorsal nerve block are effective in the early postoperative period, with low rates of complications and side effects: Grade A (133).

Evidence

Local anesthetic techniques involving a regional block or topical application can provide good analgesic efficacy in the early postoperative period (133–135). Analgesia following caudal or dorsal nerve block was equivalent and was superior to subcutaneous 'ring' block (133,136–139). Caudal and dorsal nerve block demonstrated a low failure and serious complication rate in all studies. This is in agreement with larger case series of both techniques (104,140). In some studies, a caudal block reportedly increased the time to micturition and incidence of motor block compared with dorsal nerve block and subcutaneous ring block, but this finding was not seen in other investigations (133,136–139). The ideal agent, dose, or concentration for a caudal block has not been elucidated. The use of ultrasound for dorsal nerve block has been shown to improve the efficacy and decrease the incidence of failed blocks (141) The use of subcutaneous ring block was associated with a higher failure and complication rate than caudal or dorsal nerve block (136,137). Pundendal nerve block has also been shown to provide effective perioperative analgesia for circumcision (142,143). One study compared topical local anesthesia with dorsal nerve block for 6 h postoperatively and showed no difference in analgesia (144).

Caudal neuraxial analgesic additives[1]: Ketamine + LA showed increased analgesic efficacy but also increased motor block when compared with a LA dorsal nerve block (145). The addition of ketamine or clondine conferred no additional benefit compared with LA alone in other studies (146,147).

Parenteral opioids are associated with lower analgesic efficacy and increased postoperative nausea and vomiting compared with LA techniques (135).

NSAID (Diclofenac) as a sole agent was inferior to dorsal nerve block, but the combination may decrease supplementary analgesic use compared with either technique in isolation (134).

Analgesia Table 5.5.2 Circumcision

Agent	Technique	Direct evidence
LA	Topical[a]	1+
LA	Subcutaneous 'ring' block[a]	1−
LA	Pudendal nerve block	1−
LA	Dorsal n. block	1+
LA	Caudal epidural	1+
Opioid[b]		1+
NSAIDS[b]		1+
Paracetamol[b]		1+

[a]lower efficacy than caudal epidural or dorsal nerve block.
[b]As part of a multi-modal technique.

5.5.3 Neonatal Circumcision

Neonatal circumcision is considered separately from circumcision in older children because of differences in clinical practice and evidence base. Premature neonates can experience pain and therefore require good

[1]Note on caudal additives: not all additives have undergone rigorous safety testing, and concerns regarding potential toxic effects have been expressed. See Section 6.3.

perioperative analgesia for surgical interventions. Many circumcisions are done in the *awake* neonate in the first few hours or days of life; this is reflected in the literature as studies have generally evaluated pain during the procedure. However, for neonatal circumcision, no single technique has been shown to reliably alleviate pain in the awake patient, which therefore presents a clinical challenge. Circumcision in infants and older children is invariably performed under general anesthesia (see section 5.5.1), the debate regarding the necessity for general anesthesia in the neonate remains unresolved. See sections 5.1 for the general management of postoperative pain and 5.5.1 for a further discussion of sub-umbilical surgery.

Good practice point

General anesthesia should be considered for neonatal circumcision. A multi-modal analgesic approach should include a local anesthetic technique at the time of the procedure in combination with sucrose and paracetamol.

Recommendations

LA should be used as it is superior to other techniques for circumcision pain: Grade A (148).

Dorsal nerve block is more effective than subcutaneous ring block or topical LA: Grade A (148).

When using topical local anesthetic, it must be applied correctly and sufficient time allowed for it to become effective: Grade A (148).

Evidence

Postoperative pain *after* circumcision in the neonate has not been well investigated, and available studies have all examined pain *during* the procedure in awake neonates. It has been suggested that the procedure be performed in awake infants only during the first week of life as pain scores during the procedure have been shown to increase to unacceptable levels with increasing neonatal age (149). For all techniques studied, there was a significant failure rate (148,150). The use of LA was superior to either placebo or simple analgesics and sucrose (148). Dorsal nerve block appears to be superior to subcutaneous ring block or topical local anesthesia (caudal epidural analgesia has not been studied, see (107)) and was associated with lower cortisol levels in one study, but was operator dependent and not totally reliable (148,150). Efficacy of topical local anesthetic agents was very dependent on the technique of application and time allowed (148,151,152). No increased incidence of complications was seen in one technique compared with another (148). The duration of surgery (and therefore duration of intra-operative pain) was dependent on the surgical technique with the 'Mogen Clamp' associated with faster procedures (148,150).

Analgesia Table 5.5.3 Neonatal Circumcision

Agent	Technique	Direct evidence	Indirect evidence
LA	Topical	1++	
LA	Subcutaneous 'ring' block	1++	
LA	Dorsal nerve block	1++	
LA	Caudal epidural		1+
Paracetamol[a]			1+
Sucrose[b]			1+

[a]For postprocedure pain.
[b]As part of multimodal technique.

5.5.4 Hypospadias repair

Hypospadias surgery may be either relatively superficial and minor, or more major reconstructive surgery involving the entire penile urethra may be undertaken, which will influence postoperative analgesia requirements. Some procedures are suitable for day-case surgery whilst others require hospital admission overnight or longer, with the possibility of prolonged urethral catheterisation and painful postoperative dressing changes. See sections 5.1 and 5.5.1 for the general management of postoperative pain and for a further discussion of sub-umbilical surgery.

Recommendation

LA central neuraxial or dorsal nerve block is effective reducing the need for postoperative supplementary opioid administration following hypospadias surgery: Grade A (153–158).

Evidence

Caudal LA was most commonly investigated for hypospadias repair. Good efficacy for the technique was demonstrated with a low failure and serious complication rate; this is in agreement with large case series of this technique (104–106). Bupivacaine 0.25%, 0.5 $ml \cdot kg^{-1}$ was most frequently studied, but there were few comparisons with other local anesthetics or between different concentrations or volumes. One study found that caudal ropivacaine 0.1%, 1.8 $ml \cdot kg^{-1}$,

was more effective with less motor block than ropivacaine 0.375%, 0.5 ml·kg^{-1} (159).

Caudal neuraxial analgesic additives[a]: With LA: the addition of neostigmine or diamorphine to caudal bupivacaine increased analgesic efficacy (154,157,160) but also increased the rate of nausea and vomiting in two of the studies (154,160). Adding tramadol to bupivavcaine increased the analgesic efficacy in the first 24 h postoperatively (161). In other studies, the addition of tramadol, clonidine, or sufentinil did not increase efficacy (153,162,163).

Without LA: ketamine or mixture of ketamine/alfentanil was superior to alfentanil alone, and higher doses of neostigmine increased efficacy but also increased nausea and vomiting (164,165). In general, the use of neuraxial analgesics has not been comprehensively studied, further research to identify safety profile, risk–benefit and dose are required (see also section 6.0). Only one study compared different techniques and showed that tramadol given by the caudal route demonstrated better analgesic efficacy and less postoperative nausea and vomiting than when given by the intravenous route (166).

Epidural analgesia was shown to provide good analgesia both intra- and postoperatively irrespective of the local anesthetic agent used: bupivacaine, levobupivacaine, or ropivacaine, there was an exclusion rate of 10% in one study (167) and patients having an abdominal incision were included in another (168). The addition of fentanyl to ropivacaine demonstrated increased analgesic efficacy for postoperative epidural infusions at low (0.125%) concentrations of ropivacaine (158).

Dorsal nerve block is effective for distal hypospadias repair. An investigation of the timing of dorsal nerve block either pre or postsurgery found that placing the block prior to surgery improved analgesic efficacy (169).

Spinal intrathecal neuraxial analgesia using hyperbaric 0.5% bupivacaine is effective both intra- and postoperatively. The addition of morphine to the LA increased the efficacy with no increase in adverse effects in one study (170).

Paracetamol given alongside caudal block did not improve analgesia in the first six postoperative hours compared with a caudal block alone in one study (171). Overall, there are insufficient data to evaluate the use of supplementary analgesia in either the early or late postoperative period. In clinical practice, a multi-modal analgesic technique for this procedure is suggested, with regular supplementary analgesia given in the postoperative period.

Analgesia Table 5.5.4 Hypospadias Repair

Agent	Technique	Direct evidence	Indirect evidence
LA	Dorsal n. block	1+	
LA	Caudal epidural	1+	
LA	Lumbar epidural	1+	
LA	Spinal	1−	
LA + neostigmine[a,b]	Caudal epidural	1+	
LA + opioid[b]	Caudal epidural	1+	
LA + opioid	Intrathecal	1−	
Opioid[c]			1+
NSAID[c]			1+
Paracetamol[c]			1+

[a]Note on caudal additives: not all additives have undergone rigorous safety testing, and concerns regarding potential toxic effects have been expressed. See Section 6.3.
[b]Small improvements in efficacy must be balanced against increased PONV.
[c]As part of a multi-modal technique.

5.5.5 Orchidopexy

Orchidopexy usually involves surgical exploration of the inguinal region, dissection, and traction of the spermatic cord and scrotal incision may also be required. Orchidopexy is generally performed on a day-case basis. See sections 5.1 and 5.5.1 for the general management of postoperative pain and for a further discussion of sub-umbilical surgery.

Recommendation

Caudal block is effective in the early postoperative period for orchidopexy with low rates of complications and side effects: Grade A (172–174).

Evidence

There are few studies investigating analgesia for orchidopexy alone. Postoperative analgesic requirements may be greater than that required for inguinal hernia repair (97).

LA caudal block using 1 ml·kg^{-1} of 0.125–0.25% bupivacaine or 1–1.5 ml·kg^{-1} of ropivacaine 0.15–0.225% has shown good efficacy and low complication rates (172–175). This is in agreement with large case series of this technique (104–106). It was associated with greater efficacy, less supplementary analgesic use and lower levels of stress hormones when compared with ilioinguinal nerve block plus local infiltration (172,173). There was also no difference in time to micturition, motor block or nausea and vomiting between the two techniques (172). A higher volume of local anesthetic (1 ml·kg^{-1}) was associated with less response

to cord traction, but not with improved postoperative analgesia (174).

Neuraxial analgesic additives: the addition of ketamine 0.25–1 $mg \cdot kg^{-1}$ as an adjunct to bupivacaine increased analgesic efficacy but was associated with 'short-lived psychomotor effects' at higher doses (176).

The addition of IV dexamethasone with ropivavcaine caudal block was associated with increased analgesic efficacy (177).

Transverse abdominal plane (TAP) block using plain LA, as part of a multi-modal analgesic technique, has demonstrated perioperative analgesic efficacy with no complications in a small case series (178).

Analgesia Table 5.5.5 Orchidopexy

Agent	Technique	Direct evidence	Indirect evidence
LA	Wound infiltration[a]	1+	
LA	Ilioinguinal block[a]	1+	
LA	Caudal epidural	1+	
LA	TAP block	3	
Opioid[b]			1+
NSAID[b]			1+
Paracetamol[b]			1+

[a]Less effective than caudal block.
[b]As part of a multi-modal technique.

5.5.6 Inguinal hernia repair (open)

Surgical repair of inguinal hernia is generally performed on a day-case basis. The following refers to the conventional 'open' technique, rather than laparoscopic repair that is becoming more popular. See sections 5.1 and 5.5.1 for the general management of postoperative pain and for a further discussion of subumbilical surgery.

Good practice point

The use of an ultrasound-guided technique for the placement of an ilio-inguinal nerve block may decrease the failure rate and improve analgesic efficacy.

Recommendations

LA wound infiltration, ilio-inguinal nerve block, paravertebral block, or caudal analgesia are effective in the early postoperative period: Grade A (179–184).

Evidence

Caudal block was the most commonly studied technique with good efficacy and a low failure complication rate in all studies. This is in agreement with large case series of this technique (104–106). Bupivacaine 0.25% was the most studied and compared LA, ropivacaine 0.25% was found to be equivalent in one study (185). Another study comparing different concentrations of bupivacaine with and without adjunctive opioid showed lower efficacy for 0.125% bupivacaine (186). In a study of bupivacaine 0.175% (+adrenaline 1 : 10 000), there was no difference in efficacy or side effects at volumes of between 0.7 and 1.3 $ml \cdot kg^{-1}$ (187).

Neuraxial analgesic additives: With LA; midazolam, ketamine, clonidine, fentanyl, neostigmine, adrenaline, morphine and tramadol have all been studied as adjuncts to local anesthesia for caudal block. They all show good efficacy, but evidence of overall benefit is equivocal as in most studies few patients required further analgesia following caudal block with plain LA (166,175,181,188–195). In studies where no comparison was made with plain LA: increasing the dose of ketamine also increased efficacy, but neuro-behavioral side effects were seen at higher doses (196). Increasing clonidine dose from 1 to 2 $\mu g \cdot kg^{-1}$ had limited or no effects on efficacy, time to 1st analgesia was prolonged in one study, but not in another (188,197).

Without LA: S (+) ketamine without local anesthetic was equivalent to bupivacaine + adrenaline mixture, and S (+) ketamine + clonidine mixture showed increased efficacy over ketamine alone (198,199). Another study comparing caudal with intramuscular S-ketamine showed increased efficacy in the caudal group (200). Tramadol without local anesthetic showed reduced efficacy compared with plain bupivacaine or a bupivacaine + tramadol mixture (191).

Placement of caudal block prior to surgery was also shown to have better efficacy in the postoperative period than placement at the end of surgery in one study (201).

Comparison of paravertebral block with caudal LA or intraoperative opioid (fentanyl) showed increased postoperative analgesic efficacy, patient satisfaction, and earlier hospital discharge with the paravertebral block (184,202).

Ilioinguinal nerve block shows good efficacy and safety, although a preferred agent, dose, or volume has not been demonstrated, although Levobupivacaine concentrations below 0.25% show decreased efficacy (182,203–205). High failure rates have been associated

with using landmark techniques (205,206). Ultrasound-guided techniques may increase the success rate and allow placement of the LA closer to the nerves with lower volumes being required for efficacy thereby decreasing the potential for systemic toxicity (206–208). No advantage was seen postoperatively with the addition of genitofemoral nerve block or by using a 'double shot technique' (182,203). In one study, the success rate of the block using surface landmarks was quoted as only 72% (203).

Wound infiltration is effective when compared to caudal block with plain LA or placebo, although in one study postoperative opioid use was comparatively high (179,180,209). The timing of wound infiltration, either pre or postsurgery, did not influence efficacy (180,209,210). The use of Tramadol without LA for infiltration was effective in one study (211).

When using a perioperative opioid-based regimen (without LA block), multi-modal analgesia adding both paracetamol and a NSAID is more effective than either opioid alone or opioid plus either paracetamol or NSAID (212,213).

Analgesia Table 5.5.6 Inguinal Hernia Repair (Open)

Agent	Technique	Direct evidence	Indirect evidence
LA	Wound infiltration	1+	
LA	Ilioinguinal Block	1+	
LA	Paravertebral Block	1−	
LA	Caudal Epidural	1+	
Opioid	Wound infiltration	1−	
Opioid[a]		1−	1+
NSAID[a]		1−	1+
Paracetamol[a]		1−	1+

[a]As part of a multi-modal technique.

5.5.7 Umbilical hernia repair

Umbilical hernia repair is usually regarded as a relatively minor surgical procedure, but it may be associated with significant postoperative pain. It is often undertaken on an out-patient or day-case basis. See sections 5.1 for the general management of postoperative pain.

Good practice point

A multi-modal analgesic regimen combining local anesthesia and simple analgesics perioperatively is recommended, opioid supplementation may be required. Paracetamol and/or NSAID should be continued postoperatively for at least 48 h.

Evidence

Local anesthesia techniques including wound infiltration, rectus sheath block, and paraumbilical block are effective with few complications. Ultrasound-guided rectus sheath block showed increased intraoperative analgesic efficacy when compared with wound infiltration (214). Either bupivacaine or levobupivacaine 0.25% were used in the studies, but there has been no comparison between these agents or concentrations or volumes (215–218). Ultrasound demonstrates the inter-individual variability in umbilical anatomy, its use may increase the rate of correct needle placement, improved efficacy and reduce the volume of LA required (216,218).

Analgesia Table 5.5.7 Umbilical Hernia Repair

Agent	Technique	Direct evidence	Indirect evidence
LA	Wound infiltration	2−	
LA	Paraumbilical block	3	
LA	Rectus sheath block	2−	
Opioid[a]			1+
NSAID[a]			1+
Paracetamol[a]			1+

[a]As part of a multi-modal technique.

5.6 General surgery and urology (major)

5.6.1 Intra-abdominal surgery

This group includes a heterogeneous mixture of abdominal procedures on the gastro-intestinal (GI) and genitourinary (GU) tracts including nephrectomy, pyeloplasty, ureteric reimplantation, and cystoplasty for all of which a significant level of postoperative pain is expected. Intravenous opioid techniques or epidural analgesia are acceptable for postoperative pain management; in clinical practice, supplementary analgesia with NSAID and paracetamol is usually also administered.

Appendicectomy and fundoplication are considered separately in sections 5.6.2, 5.6.3 and laparoscopic techniques in section 5.7. See also section 5.1 for general management of postoperative pain.

Good practice point

Multimodal analgesia using parenteral opioids, central neuraxial analgesia together with systemic NSAIDs

and paracetamol should be used unless specifically contraindicated.

Recommendations

Intravenous opioids either as continuous infusion, NCA or PCA are effective following major abdominal surgery: Grade A (219–223).

Epidural analgesia with LA should be considered for major abdominal surgery. The addition of neuraxial clonidine or opioid may further improve analgesia, but side effects may also be increased: Grade B (168,224–229).

Evidence

There is a considerable descriptive literature (predating the time limits of this guideline 1996–2011) describing the use of opioid infusions, PCA, NCA, and LA epidural infusion with or without opioid for major surgery such that these techniques have become part of everyday practice. For suitable regimens, see section 6. Paravertebral LA block has also been described and is a feasible alternative. There are very few well-designed clinical trials comparing these analgesic techniques. A variety of surgical procedures are included in most studies, the exact surgical incision employed is frequently not stated.

Intravenous opioids as a continuous infusion, PCA or NCA are effective following abdominal surgery: the analgesic response is a function of dose and developmental age (219–223). See Section 6.1 for information on doses and regimens.

Continuous epidural analgesia with LA is acceptable. Bupivacaine, ropivacaine, and levobupivacaine have been shown to be effective in a variety of infusion concentrations and dose rates (168,224,226,230,231).

Epidural LA + opioid also provides good analgesia. Morphine, fentanyl, hydromorphone, and diamorphine have been the most frequently described; the side effect profile depends on the dose and particular opioid that is used (168,226,228,232).

Single-shot caudal epidural LA + clonidine has been compared to LA alone, LA + opioid, LA + dexmedetomidine and clonidine alone. Clonidine causes dose-dependant sedation and hypotension. Clonidine or clonidine + LA were equally effective as part of a multimodal strategy in combination with ketoprofen (233). Clonidine (1–2 $\mu g \cdot kg^{-1}$) + LA has fewer side effects compared to opioid + LA, efficacy may also be lower (228,234). Caudal epidural clonidine 2 $\mu g \cdot kg^{-1}$ or dexmedetomidine 2 $\mu g \cdot kg^{-1}$ with LA prolonged the duration of LA without increasing side effects (235).

Epidural opioid (without LA):

Single doses of epidural opioid can improve postoperative analgesia and reduce requirements for ongoing analgesia (236,237). Intermittent epidural morphine was superior to intramuscular morphine in one study (238), but is less effective than LA containing (bupivacaine + fentanyl) infusion (224).

Peripheral nerve blocks (PNB): There is an increasing interest in the use of single-shot and continuous peripheral nerve blocks. Paravertebral block is feasible for abdominal surgery and has been shown to decrease opioid requirements following appendicectomy, see Section 5.6.2 (239,240). Transversus abdominis plane (TAP) block is feasible for abdominal surgery in neonates and children and appears to provide satisfactory analgesia in some circumstances (241–243). A systematic review in adults and children that included TAP and rectus sheath block did not draw conclusions regarding the efficacy of these techniques because of the small number of studies available (244). See also Sections 5.5.1, 5.6.2 and 5.7.

Analgesia Table 5.6.1 Abdominal surgery

Agent	Technique	Direct evidence	Indirect evidence
LA	Epidural	1+	
LA	Paravertebral block	1+	
	TAP block	2–	
LA + opioid	Epidural	1+	
LA + clonidine	Epidural	1+	
Opioid	Epidural	1+	
Clonidine	Epidural	1–	
Opioid	Intravenous	1+	
NSAID[a]		1–	
Paracetamol[a]			1+

[a]As part of a multimodal technique.

5.6.2 Appendicectomy (open)

Appendicectomy is the most common indication for laparotomy in children. Under normal circumstances, this procedure is performed through an incision in the right lower quadrant. In the majority of cases, appendicectomy will be performed as an emergency or unplanned procedure. See also sections 5.6 and 5.6.1 for information on the general management of postoperative pain, and a further discussion of analgesia following abdominal surgery.

Good practice point

Wound infiltration with LA following appendicectomy is a simple procedure that may be of benefit in the early postoperative period as part of a multimodal analgesic technique.

Recommendation

PCA combined with NSAID is effective for postappendicectomy pain: grade B (245).

Evidence

Intravenous opioids as a continuous infusion, PCA or NCA, together with a multimodal analgesic strategy including LA wound infiltration, NSAID and paracetamol is currently suggested practice following appendicectomy (245–250).

Morphine PCA has been previously shown to be effective, supplementation with NSAID improves analgesia, particularly for pain on movement (245). The addition of ketamine to morphine did not improve analgesia in one study and neurobehavioral side effects were increased (248). Antiemetic additives to the opioid such as droperidol or ondansetron offered no advantage but may increase side effects (247,251).

Wound infiltration with LA has previously been found to be of benefit (252), but results from more recent studies are inconclusive. Neither pre nor postincision bupivacaine 0.25–0.5% reduced postoperative morphine requirement in the first 24 h when compared with placebo or no infiltration (250,253). Bupivacaine 0.25% 0.5 $ml \cdot kg^{-1}$ may not confer additional benefit in children receiving effective multi-modal analgesia with opioid, NSAID, and paracetamol (254). However, preincision bupivacaine followed by infiltration of the muscle layer on closure reduced pain scores for up to 48 h in another study that included children and adults (255).

Paravertebral block reduced time to first dose and total postoperative opioid requirements compared to placebo (240).

TAP block reduced pain scores and morphine requirements in first 24 h compared to placebo (243).

Analgesia Table 5.6.2 Appendicectomy

Agent	Technique	Direct evidence	Indirect evidence
LA*	Wound infiltration	1–	
	Paravertebral	1+	
	TAP Block	1+	
Opioid	Intravenous	1+	
NSAID[a]		1+	
Paracetamol[a]			1+

[a]As part of a multimodal technique.

5.6.3 Fundoplication (open)

This procedure usually involves an incision of the upper abdomen utilising either a midline, transverse supraumbilical, or left sub-costal approach. Increasingly laparoscopic techniques have been used for fundoplication, see section 5.7. The patient population is diverse, including significant numbers of children with neurodevelopmental delay and communication difficulties, which may influence the choice of analgesic regime. See also sections 5.1 and 5.6.1 for information on the general management of postoperative pain, and a further discussion of analgesia following abdominal surgery.

Good practice point

Multimodal analgesia using parenteral opioids or epidural analgesia together with systemic NSAIDs and paracetamol should be used unless specifically contraindicated.

Recommendation

Epidural LA + opioid is effective and may be associated with improved clinical outcome in selected patients following fundoplication: grade D (256–258).

Evidence

Some of the studies quoted have included other major procedures as well as fundoplication. There are no prospective studies comparing analgesic techniques following open fundoplication.

Epidural analgesia has been favored following fundoplication as this group of patients is at high risk of respiratory complications and includes significant numbers with neurodevelopmental delay (258–260).

Epidural LA: Ropivacaine without opioid provided satisfactory analgesia for neonates and infants after major thoracic and abdominal surgery including four patients following fundoplication (231).

Epidural LA + opioid: buivacaine + fentanyl appears to be effective; higher pain scores were noted in patients who had had fundoplication in one of the studies but overall the regimen was considered to be 'satisfactory' (257,260).

Epidural clonidine or LA + clonidine: both were found to be effective for a mixed surgical group as part of a multimodal strategy including ketoprofen, although after fundoplication ($n = 9$) there was an increased need for supplementary opioid on the first postoperative night (233).

Intravenous opioid by continuous infusion PCA or NCA appears to be effective, but may be inferior for nonpain outcomes: see 'epidural analgesia vs parenteral opioid' below (256,261,262).

Epidural analgesia vs parenteral opioid.

Two retrospective observational studies have found that duration of hospital stay is prolonged in patients selected for opioid analgesia even when spinal deformity patients (scoliosis) were excluded in one study (256,258).

Analgesia Table 5.6.3 Fundoplication (open)

Agent	Technique	Direct evidence	Indirect evidence
LA	Epidural	3	
LA + opioid	Epidural	3	
LA + clonidine[a]	Epidural	3	
Clonidine[a]	Epidural	3	
Opioid[a]	Intravenous	1+	
NSAID[a]		1+	
Paracetamol[a]		1+	

[a]As part of a multimodal technique.

5.6.4 Major urology

This category has been included because studies have used a combination of different urological procedures as the operative model, for example pyeloplasty, nephrectomy, heminephrectomy, hypospadias, bladder augmentation/reconstruction, ureteric reimplantation. Postoperative pain is unlikely to be equivalent following each of these different procedures, but they are not uniformly distributed between studies, and the numbers of individual procedures in each study are often low, thereby making it impractical to look at each procedure in isolation. See section 5.1 for the general management of postoperative pain.

Good practice point

Multimodal analgesia using parenteral opioids or regional analgesia together with systemic NSAIDs and paracetamol should be used unless specifically contraindicated.

Evidence

LA techniques are commonly used perioperatively for major urological surgery. Comparison with parenteral opioid techniques is limited, and little good evidence exists with regard to the optimum analgesic regimen.

Epidural LA ± opioid: For a variety of urological procedures, perioperative ropivacaine infusions, with or without opioid, have shown good analgesic efficacy with low pain scores and complication rates (263,264). Comparisons of fentanyl or sufentanil added to ropivacaine, and fentanyl or butorphanol added to bupivacaine showed no difference in efficacy or pain scores between these regimens (229,263).

Epidural LA vs Parenteral Opioid: Comparison of postoperative epidural ropivacaine infusions with regular bolus tramadol or oxycodone plus paracetamol and NSAID showed no difference in pain scores up to 48 h but increased rescue analgesia between 48 and 72 h (264).

Caudal neuraxial analgesic additives: In children undergoing ureteric reimplantation, caudal analgesia with LA + clonidine or opioid was effective. There was no difference in efficacy or pain scores from adding clonidine, morphine, or hydromorphone to caudal ropivacaine 0.2% + epinephrine, patients receiving clonidine experienced fewer side effects (234).

Paravertebral Block: Use of a 'single-shot' intraoperative paravertebral block with levobupivacaine and regular paracetamol postoperatively was associated with low pain scores and low opioid use in the early postoperative period in patients undergoing major renal surgery (239).

Wound Infiltration: A multimodal analgesic technique using LA infiltration alongside opioids, NSAID, and paracetamol was associated with low pain scores in children undergoing pyeloplasty and ureteric reimplantation (265,266).

Analgesia Table 5.6.4 Urological Surgery

Agent	Technique	Direct evidence	Indirect evidence
LA	Epidural	1–	
LA + opioid	Epidural	1–	
LA	Caudal epidural	1–	
LA	Paravertebral block	2–	
LA[a]	Wound infiltration	3	
Opioid[a]	Intravenous	3	1+
NSAID[a]		3	1+
Paracetamol[a]		3	1+

[a]As part of a multimodal technique.

5.7 Laparoscopic surgery

There has been a dramatic increase in the amount of pediatric laparoscopic surgery in the last decade. This is performed mainly through the body cavities (chest and abdomen) or potential spaces. Inguinal hernia repair, appendicectomy, fundoplication, urological and adrenal surgery are examples. For general management of postoperative pain, see section 5.1.

Good practice points

Infiltration of port sites with LA as part of a multimodal analgesic strategy may reduce postoperative pain following laparoscopy.

Although overall postoperative analgesic requirements appear to be reduced following laparoscopy, pain may be equivalent to the equivalent open procedure in some circumstances, particularly during the first 24 h.

Evidence

Advantages of laparoscopic surgery may include faster recovery and overall reduction in pain and use of opioid analgesia in comparison with the open surgical counterpart (246,267–272). Although the overall duration of postoperative pain appears to be reduced, analgesic requirements may be at least as great on the first postoperative day as the equivalent open procedure (261,267,273–275). The use of robotic laparoscopic techniques may also decrease postoperative opioid requirements after ureteric reimplantation surgery (276). The anatomical approach to laparoscopic surgery has not been shown to effect analgesic requirements (277,278).

Multimodal analgesia including LA infiltration, opioid, NSAID, and paracetamol is suitable, and the use of carefully designed protocols may improve efficacy (279). Demand-led opioid regimens such as PCA or NCA are feasible and effective for some procedures and require further evaluation (246,262).

LA infiltration of port sites when combined with NSAID provided equivalent analgesia to caudal block for minor diagnostic and therapeutic laparoscopic procedures and to TAP block following appendicectomy (280,281). Use of aerosolised bupivacaine after port insertion, as part of a multimodal analgesic regimen, demonstrated some opioid sparing effect (282).

Perioperative regional LA techniques have also been shown to be effective and again require further evaluation (271,279). Little good evidence exists with regard to the optimum analgesic regimen.

Analgesia Table 5.7 Laparoscopic surgery

Agent	Technique	Direct evidence	Indirect evidence
LA*	Infiltration	1–	
LA*	Aerosolised	3	
LA	Caudal	1–	
Opioid	Parenteral/oral	3	
NSAID[a]		1–	
Paracetamol[a]		3	

[a]As part of a multimodal technique.

5.8 Orthopedics, spinal and plastic surgery

5.8.1 Lower limb surgery

The surgery covered in this section ranges from relatively minor single site orthopedic surgery to more major procedures such as multiple level osteotomies.

The population of patients requiring femoral and pelvic osteotomies includes those suffering from cerebral palsy; pain in this population can also precipitate painful muscle spasm requiring specific management with benzodiazepines.

Multimodal analgesia is suitable: there is particularly extensive experience of the use of local anesthetic techniques for this type of surgery. Concerns have been expressed that NSAIDs may inhibit new bone growth following orthopedic surgery; this is addressed below.

Good practice point

There is no evidence from studies in children that NSAIDs have a deleterious effect on bone fusion. The analgesic benefit of short-term NSAID use has been demonstrated and may frequently outweigh any hypothetical risk.

Recommendations

Peripheral nerve blocks provide superior analgesia and are associated with fewer adverse effects compared with intravenous opioids: Grade B (283,284).

Epidural opioids are effective, reduce the dose requirements of local anesthetic, and rescue IV opioids but increase the incidence of side effects: Grade B (259,285,286).

Continuous peripheral nerve blocks are feasible, effective, and safe and are associated with lower pain scores: Grade B (287–295).

Epidural techniques are associated with lower pain scores than intravenous opioid analgesia: Grade C (237,257,296,297).

Systemic paracetamol and NSAID reduce intravenous opioid requirements: Grade C (298,299).

Evidence

Studies have shown epidural analgesia using opioids, local anesthesia or a mixture of the two are effective but differences in efficacy and side effects between regimens are observed. Epidural opioids improve analgesia but side effects are more frequent. The side effect profile may be related to the individual properties of specific opioids: morphine, fentanyl, and hydromorphone were of comparable analgesic efficacy in one study; respiratory depression, somnolence, and retention of urine were higher in the morphine group; PONV and urinary retention had the lowest incidence with hydromorphone (285). Single-dose epidural morphine was equianalgesic with increasing dose (11.2, 15, and 20 $\mu g \cdot kg^{-1}$), but the incidence of PONV increased with dose (300). In a study comparing bupivacaine + fentanyl with bupivacaine (both with adrenaline), the fentanyl group had superior analgesia and did not require rescue opioid but had a higher incidence of PONV, whereas the bupivacaine group required more bupivacaine and 10/26 (38%) required rescue opiates and antiemetic therapy, itching only occurred in the fentanyl group (286).

Epidural vs peripheral nerve block

A comparison of continuous epidural block with continuous popliteal nerve block for major foot surgery showed no difference in pain or rescue analgesia, but adverse effects and patient satisfaction were improved with peripheral nerve block (290). In congenital club foot surgery, a comparison of single-shot caudal anesthesia with single-shot peripheral nerve blocks (combined sciatic femoral, combined sciatic saphenous, and saphenous combined with local infiltration) showed no difference in the duration of analgesia and no difference in morphine consumption within the first 24 h, there was no difference in the incidence of nausea and vomiting between any of the groups (301). Single-shot Psoas Compartment Block showed moderate reduction in postoperative opioid requirements compared to caudal epidural following open hip reduction or osteotomy (302).

Epidural compared with Intravenous techniques

In a comparison between patient-controlled epidural analgesia (PCEA) with lidocaine, and nurse-controlled IV fentanyl, pain scores (unvalidated method), and PONV were lower in the epidural group (297). A single dose of epidural morphine 30 $\mu g \cdot kg^{-1}$ reduced postoperative PCA morphine use, and VAS scores were also lower in the epidural morphine group, and there was no difference in the incidence of severe pruritus or PONV (237).

Peripheral nerve block vs intravenous techniques

Comparisons between peripheral nerve blocks and intravenous morphine in pelvic osteotomy (283) and patella realignment surgery (284) demonstrate reduced pain scores, reduced morphine consumption and a reduction in the incidence of sedation with the use of peripheral nerve blocks.

A number of successful series of peripheral nerve blocks have been described, including popliteal nerve block (288,290,292–294,303), fascia iliaca compartment block (288,303,304), sciatic nerve block(289,291,295,305), psoas compartment block (287,293), and femoral nerve block (284,304).

Continuous LA infusion vs PCRA/PCEA

PCRA (Ropivacaine 0.2%) showed similar efficacy to a continuous regional technique, with a lower total dose of LA for popliteal and fascia iliaca blocks (303). In a comparison of PCEA vs CEA, again efficacy was similar and a lower dose of LA used (306).

Systemic analgesia with NSAID and paracetamol can be combined with intravenous opioid or regional analgesia. In one study, a combination of paracetamol and ketoprofen significantly decreased pain scores and IV morphine requirements compared to either drug alone (299). In a case series of patients undergoing club foot surgery and long bone osteotomy, ketorolac reduced IV morphine usage and associated GI effects

(298). Ketorolac did not influence bony union in a case series of lower limb osteotomies (307).

Adjuvant analgesics

The use of intravenous magnesium (50 $mg \cdot kg^{-1}$ bolus followed by an infusion of 15 $mg \cdot kg^{-1} \cdot h^{-1}$) reduced postoperative pain scores and analgesic consumption in children with cerebral palsy undergoing femoral osteotomy.

Analgesia Table 5.8.1 Lower Limb surgery

Agent	Technique	Direct evidence	Indirect evidence
LA	Peripheral nerve block	1+	
	Caudal Epidural	1–	1–
	Lumbar Epidural	1+	
Opioid	IV infusion	1+	
NSAID[a]		1+	
Paracetamol[a]		1+	
Clonidine	Peripheral nerve block	3	

[a]As part of a multi-modal technique.

5.8.2 Upper limb surgery

Surgery on the upper limb is most commonly performed for plastic and orthopedic procedures of hand and forearm, often following trauma. Local anesthesia of the brachial plexus prior to surgery is frequently used. There is some controversy regarding the most safe and reliable approach to the brachial plexus. See section 5.1 for the general management of postoperative pain.

Recommendations

Brachial plexus blocks provide satisfactory analgesia for hand and forearm surgery extending into the postoperative period: Grade B (308–313).

The axillary, infraclavicular, supraclavicular, and interscalene approach are feasible and effective: Grade B (291,294,308,310–315).

Evidence

Analgesia following upper limb surgery has not been well studied, and few investigations of postoperative pain management have been undertaken. Brachial plexus block appears to be effective, but differences between techniques have not been investigated. The axillary approach to the brachial plexus is theoretically less likely to lead to accidental pneumothorax. There are no comparisons between brachial plexus block and other alternatives such as intravenous opioid.

Axillary brachial plexus block was the most studied approach; postoperatively patients were generally managed with oral analgesia. There was no difference in postoperative efficacy (time to 1st analgesia, analgesic consumption, pain score) between 0.2% ropivacaine and 0.25% bupivacaine when used for axillary brachial plexus block (312). There was no benefit to using a fractionated dose of LA compared to a single injection for axillary brachial plexus block, nor in placing the block prior to or after surgery (309,316).

Other studies have examined the feasibility of the different approaches to brachial plexus block. The infraclavicular (311,313,315), the supraclavicular approach (310), and the interscalene approach (291) are effective, and there were no incidences of pneumothorax in these studies (412 patients).

A comparison between peripheral nerve block at the wrist and intravenous alfentanil demonstrated superior analgesia and a reduction in adverse events in the block group (317).

Analgesia Table 5.8.2 Upper Limb surgery

Agent	Technique	Direct evidence	Indirect evidence
LA	Brachial plexus block	1+	
Opioid	Intravenous		1+
	Oral		1+
NSAID[a]			1+
Paracetamol[a]			1+
Clonidine	Brachial plexus block	3	

[a]As part of a multi-modal technique.

5.8.3 Spinal surgery

Surgery to correct spinal deformity requires extensive exposure of the spine which may be achieved posteriorly, anteriorly via thoracotomy or thoraco-abdominal approach, or by a combined anterior–posterior approach. Postoperative pain can be severe and prolonged, necessitating the use of potent intravenous or neuraxial analgesic techniques for 3–5 days postoperatively. The use of intravenous opioid analgesia has not been well studied; however, the success of neuraxial techniques in controlling postoperative pain in children has led to an interest in their use for spinal surgery.

The patient population requiring spinal surgery includes healthy adolescents and patients with severe underlying medical conditions such as Duchenne's muscular dystrophy and cerebral palsy. The choice of analgesic technique will be influenced by both patient

and surgical factors in addition to local circumstances, for example, neuraxial techniques are not suitable for some patients. The involvement of the surgeon in the choice of analgesic technique is especially important in spinal surgery as it must also enable early and frequent assessment of neurological function, and epidural LA is not usually administered following surgery until normal neurological function has been demonstrated. See section 5.1 for the general management of postoperative pain.

Good practice point

There is no evidence from studies in children that NSAIDs have a deleterious effect on bone fusion. The analgesic benefit of short-term NSAID use has been demonstrated and may frequently outweigh any hypothetical risk.

Recommendations

Epidural techniques produce a modest improvement in pain control, compared with intravenous opioids in patients undergoing corrective surgery for adolescent idiopathic scoliosis: Grade B (318–322).

Intrathecal opioids decrease intra-operative blood loss and IV opioid consumption postoperatively. The duration of action is 18–24 h: Grade C (318,323–326).

Dual catheter epidural techniques should be considered, as this permits coverage of multiple spinal levels: Grade C (319,327–329).

The use of LA + lipophilic opioid in the epidural space with a single epidural catheter does not show an analgesic benefit over intravenous opioid techniques: Grade C (330,331).

The use of LA + hydrophilic opioids in the epidural space has a favorable analgesic profile compared with IV opioid, but at the expense of increase adverse effects: Grade D (332,333).

Evidence

The majority of studies have been conducted in adolescents, and some studies have also included young adults up to the age of 22 years. Neuraxial techniques have been the most investigated. Intrathecal (IT) opioids: single doses of IT opioids can reduce intraoperative blood loss and postoperative analgesic requirements. IT morphine plus sufentanil decreased intra-operative blood loss compared with IV sufentanil (323). IT morphine 5 $\mu g \cdot kg^{-1}$ also decreased intra-operative blood loss compared with 2 $\mu g \cdot kg^{-1}$ IT or saline controls (324). The time to first analgesic use, 6–24 h postoperatively, was significantly increased in proportion to dose of IT morphine in these studies (323,324,334). Pain scores were also lower with intrathecal morphine (318,324). However, the use of a high-dose intrathecal opioid regime (15 $\mu g \cdot kg^{-1}$ morphine + 1 $\mu g \cdot kg^{-1}$ sufentanil) did not improve analgesic efficacy or enhance the reduction in blood loss compared with a low-dose regimen (5 $\mu g \cdot kg^{-1}$ morphine + 1 $\mu g \cdot kg^{-1}$ sufentanil) (325).

Several studies have found no increase in respiratory depression with IT opioids up to a maximum dose of 20 $\mu g \cdot kg^{-1}$ of morphine compared with intravenous techniques (323,324), and no difference in level of sedation, nausea and vomiting or pruritus (324). However, intrathecal morphine in excess of 20 $\mu g \cdot kg^{-1}$ was associated with respiratory depression (326). IT opiates did not affect the ability to monitor spinal sensory evoked potentials (SSEPs) (335).

A meta-analysis of epidural analgesia in adolescent scoliosis surgery demonstrated a statistical, but clinically modest improvement in pain scores in patients receiving epidural analgesia compared with intravenous opioids on all first three postoperative days. One hundred and twenty patients from four studies were included in the analysis which also concluded that patient satisfaction was higher in the epidural group. The papers included in the meta-analysis differ in the regimens used: two papers report the use of a single catheter midthoracic epidural infusion of bupivacaine and fentanyl and show no difference in pain sores compared PCA morphine (330,331). The remaining two papers report the use of a dual catheter technique infusing ropivacaine without opiod in patients following posterior (329) and anterior (319) spinal surgery. Significantly lower pain scores were recorded compared with continuous IV morphine infusion. A prospective comparison between PCEA with bipvacaine 0.1% and hydromorphone 10 $\mu g/ml^{-1}$ and PCA hydromorphone demonstrated a reduction in pain scores in the epidural group. There have also been several retrospective series demonstrating reduced pain scores with epidural analgesia compared with IV opioid: A single epidural catheter infusing bupivacaine with hydromorphone compared with a group receiving PCA morphine (613 patients); the epidural group had a higher incidence of side effects (333). Dual epidural catheters infusing 0.1% bupivacaine with fentanyl 2 $\mu g \cdot ml^{-1}$ compared with an opioid PCA, no difference in adverse effects (322). Single epidural infusing bupivacaine 0.1% and hydromorphone compared with PCA morphine compared with intrathecal and PCA morphine: intrathecal morphine controlled pain equally as

well as the epidural technique for the first 24 h, but epidural was superior at 36 and 48 h (138 patients) (318). Case series have demonstrated effective analgesia with the following regimes: bupivacaine 0.0625–0.1% with fentanyl, hydromorphone or morphine, 0.1% ropivacaine with hydromorphone, bupivacaine 0.0625–0.125% with morphine, bupivacaine 0.0625% with fentanyl and clonidine (332,336–339). Several authors commented that placement of the epidural catheter by direct visualisation during surgery was important.

Both 0.0625% bupivacaine with fentanyl and with clonidine and ropivacaine with hydromorphone have also been reported as successful using a dual catheter technique (327,328). Epidural analgesia may be associated with a more rapid return in GI function (318,330). The use of an epidural technique did not compromise neurological assessment (336). There was one report of a wound infection occurring in a patient receiving epidural analgesia (330) but no reports of epidural hematoma or abscess.

NSAIDS: There have been two retrospective reviews looking at the use of NSAIDS following spinal surgery. There was no difference in the incidence of nonunion in patients who had received ketorolac (221 patients) compared to controls (306 patients) (333,340).

Adjuvant analgesics: The use of gabapentin (15 $mg \cdot kg^{-1}$ preoperatively followed by 5 $mg \cdot kg^{-1}$ tds for 5 days) reduced opioid consumption on postoperative days 1 and 2 and reduced pain scores on day 1 compared with placebo, no difference was seen beyond day 2 and no difference was seen in side effects (341). No difference was seen in pain scores or morphine consumption when low-dose ketamine was administered intra-operatively (0.5 $mg \cdot kg^{-1}$ loading dose followed by an infusion of 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) compared with placebo (342). A retrospective review of the addition of dexmedetomidine (0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$) to PCA morphine was unable to demonstrate a significant difference in pain scores or morphine consumption compared with PCA morphine alone (343).

Analgesia Table 5.8.3 Spinal surgery

Agent	Technique	Direct evidence	Indirect evidence
LA	Thoracic Epidural	1+	
LA	Lumbo-thoracic 2 Catheter	1+	
Opioid	Intrathecal	1+	
Opioid	IV infusion	1+	
Clonidine	Epidural	3	
NSAID[a]			1+
Paracetamol[a]			1+
Gabapentin		1+	

[a]As part of a multi-modal technique.

5.8.4 Cleft lip and palate and related procedures

This section includes a range of procedures such as repair of Cleft Lip and Palate, Otoplasty, and Alveolar bone grafting. See section 5.1 for the general management of postoperative pain.

Recommendation

Infraorbital nerve block provides effective analgesia for cleft lip repair in the early postoperative period: Grade A (344–348).

Evidence

The evidence base supporting the efficacy of analgesic strategies is weak for this group of procedures and postoperative analgesic requirements are not clear. Many patients appear to be successfully managed with intraoperative local anesthesia followed by NSAIDs, paracetamol, and low doses of opioid postoperatively.

Cleft Lip Repair: infra-orbital nerve block for cleft lip surgery is feasible, and studies have demonstrated lower pain scores in patients who received infra-orbital nerve block compared with IV fentanyl (347,348) peri-incisional infiltration of local anesthetic (344,345) and rectal Paracetamol (346). Blocks were performed with 0.25% bupivacaine in all these studies. The addition of opioids pethidine or fentanyl significantly prolonged the duration of the block in two studies (349,350). Clonidine added to bupivacaine resulted in a moderate improvement in postoperative analgesia in another (351).

Cleft Palate Surgery: Local infiltration (352), palatine nerve block (353), and bilateral suprazygomatic maxillary nerve block (354) have been associated with low pain scores following cleft palate repair. The effect of NSAIDs on peri-operative bleeding was reviewed in one small case series (20 patients), and there was no effect associated with diclofenac 1 $mg \cdot kg^{-1}$ b.d. (355).

Alveolar Bone Graft: Morphine PCA requirements are low (< 0.4 $mg \cdot kg^{-1}$), and there was no improvement in analgesic efficacy with the addition of IV ketorolac 0.5 $mg \cdot kg^{-1}$ qid (356). Continuous infusion of bupivacaine (357,358) and the placement of a bupivacaine-soaked absorbable sponge (358) have been used to reduce pain from the iliac crest donor site.

Otoplasty: regional nerve blockade with bupivacaine 0.5% showed no improvement in analgesia compared with local infiltration of the operative field with Lidocaine 1% and adrenaline (359).

Analgesia Table 5.8.4 Plastic surgery procedures of head and neck

Agent	Technique	Direct evidence	Indirect evidence
LA	Local infiltration	1+	
LA	Infraorbital nerve block[a]	1+	
Opioid[b]			1+
NSAID[b]			1+
Paracetamol[b]			1+

[a]Repair of cleft lip alone.
[b]As part of a multi-modal technique.

5.9 Cardiothoracic surgery

5.9.1 Cardiac surgery (sternotomy)

Classically, cardiac surgery with cardiopulmonary bypass (CPB) will involve division of the bony sternum to obtain access to the heart and great vessels. Anticoagulation with heparin is maintained throughout CPB, which has implications for the use of regional techniques. Postoperative patients are nursed in ICU areas, often with a short period of mechanical ventilation prior to extubation of the trachea. Postoperative analgesia with intravenous opioids, most frequently morphine or fentanyl, has been standard practice for more than 20 years in many institutions. See section 5.1 for the general management of postoperative pain.

Recommendation

Epidural and intrathecal techniques with opioid and/or LA are effective for sternotomy pain, but only marginal benefits have been demonstrated, and there are insufficient data concerning the incidence of serious complications: Grade B (360–368).

Evidence

Intravenous opioids are the standard to which other analgesic techniques are to be compared. A comparison of morphine and tramadol NCA found no difference in efficacy between the two, although tramadol caused less sedation in the early postoperative period (369).

There has been an increasing interest in regional analgesic techniques because of their potential to reduce stress responses and facilitate earlier tracheal extubation with possible improvements in clinical outcome and economic cost reduction. The relatively small size of studies precludes accurate prediction of very rare but serious side effects such as epidural hematoma and consequent neurological damage.

Intrathecal opioid: morphine or fentanyl produce equivalent analgesia (and side effects) to intravenous morphine with lower overall analgesic consumption (364,365).

Intrathecal opioid + LA: improved pain scores compared with bolus IV fentanyl alone with lower overall fentanyl consumption but no difference in opioid related side effects (366).

Epidural: case series have demonstrated the feasibility and efficacy of epidural catheter techniques from caudal, lumbar or thoracic approaches with few and modest improvements in outcomes (360–362,368). There is a single case report of epidural hematoma requiring surgical decompression in an 18-year-old with TEB who remained anticoagulated following aortic valve surgery (370).

NSAIDS: ketorolac commenced 6 h postoperatively did not increase postoperative bleeding, nor affect IV morphine requirements or reduce time to extubation in one study (371).

Analgesia Table 5.9.1 Cardiac Surgery (sternotomy)

Agent	Technique	Direct evidence	Indirect evidence
LA	Caudal epidural catheter	3	
LA	Thoracic epidural (TEB)	1–	
LA	Intrathecal (SAB)	1–	
Opioid	IV infusion	1+	
Opioid	Caudal	2–	
Opioid	Thoracic epidural (TEB)	2–	
Opioid	Intrathecal	1+	
NSAID[a]			1+
Paracetamol[a]			1+

[a]As part of a multi-modal technique.

5.9.2 Thoracotomy

Access to the lungs, pleura, and intrathoracic structures is obtained by an intercostal incision and separation and retraction of the ribs. Typical procedures include ligation of patent ductus arteriosus (PDA) resection of aortic coarctation, lung biopsy, or partial resection, pneumonectomy, repair of tracheoesphageal fistula. Considerable pain can be expected following classical thoracotomy incision. Recently, VATS (video assisted thoracoscopic surgery), a minimally invasive technique, has been used for some relatively minor thoracic procedures, for example lung biopsy or smaller lung resections.

Good practice point

A multi-modal analgesic approach, including a local anesthetic technique and/or opioid with NSAID and paracetamol, is suitable for postthoracotomy pain.

Recommendation

Epidural analgesia is effective for postthoracotomy pain: Grade D (225,226,231,257,372).

Evidence

Thoracotomy is frequently included in studies of analgesia for major surgery in combination with other procedures such as abdominal and spinal surgery, making interpretation of findings difficult. Either epidural analgesia or intravenous opioids as part of a multimodal strategy including NSAID and paracetamol have been used extensively for postthoracotomy pain. Paravertebral block has also been described.

There are few studies comparing regional and systemic techniques directly, or with other more novel regimens. Although it might be anticipated that pain following VATS would differ from classical thoracotomy, there are no studies exploring this issue.

Epidural analgesia is frequently recommended for postthoracotomy pain; however, there is no conclusive evidence that any particular regimen is more effective.

Epidural LA: plain bupivacaine and ropivacaine solutions have been found to be effective for major abdominal and thoracic surgery in neonates and infants (225,231). Analgesia was reported as equivalent in a case series (272 patients, 29 thoracic) comparing children who received either plain ropivacaine or bupivacaine + diamorphine as part of a multimodal analgesic strategy (226).

LA + opioid: bupivacaine with fentanyl, morphine, diamorphine, or other opioids is effective for postthoracotomy pain, by continuous infusion or PCEA (226,257,372,373).

Epidural opioid without LA: single-dose thoracic epidural morphine was equivalent to intravenous morphine infusion in the first 24 h after thoracotomy (374). Single-dose caudal morphine with or without LA was less effective than thoracic epidural Morphine + LA infusion; infusion patients also had better nonpain outcomes, for example earlier oral intake, less PONV, and shorter ICU stay (373).

Intrathecal opioid as part of a multimodal technique has been described in a small case series (375).

Paravertebral block has been described as effective in a number of small case series of neonates, infants, and children (376–382). There have been no comparisons with other techniques.

Intercostal nerve block: increased the time to further analgesia when compared with a single dose of pethidine at skin closure (383).

Opioids: intravenous infusion of opioid is frequently used for severe postoperative pain including postthoracotomy (384,385). PCA/NCA has been described in studies that have included a small number of postthoracotomy patients (220,221,223). Data on the efficacy of opioids for thoracotomy are inadequate to allow conclusive evaluation, and the role of multimodal analgesia has also not been sufficiently evaluated. In a comparison of PCA and continuous infusion of morphine without supplementary NSAID and paracetamol, there was no difference between the groups, but 20–40% of patients in each group had pain scores in the 'severe' range on the first postoperative day (220).

Analgesia Table 5.9.2 Thoracotomy

Agent	Technique	Direct evidence	Indirect evidence
LA	Thoracic epidural[a]	3	
LA	Paravertebral block	3	
LA	Intercostal block[b]	3	
LA + opioid	Thoracic epidural[a]	3	
Opioid	Thoracic epidural[c]	1–	
Opioid	Intrathecal[b]	3	
Opioid	Intravenous	2–	
NSAID[b]			1+
Paracetamol[b]			1+

[a]Caudal, lumbar and thoracic catheter insertion sites.
[b]As part of a multi-modal technique.
[c]1st 24 h.

5.10 Neurosurgery

Neurosurgical procedures in children include drainage of hydrocephalus and insertion or replacement of an extra cranial shunt, craniotomy, craniofacial surgery, and surgery for intracranial aneurism or other vascular malformation. There has been little investigation of analgesic requirements or analgesia for this group of patients, but it is frequently asserted that severe postoperative pain is not a prominent feature, even following major neurosurgical interventions, this has been disputed (386). Postoperatively, many neurosurgical patients are admitted to ICU or high dependency areas for monitoring; opioid analgesia must be used judiciously as excessive sedation may mask signs of acute changes in intracranial pressure or interfere with the patient's ability to co-operate with neurological assessments. As the risk of postoperative bleeding is rela-

tively high and potentially disastrous following some procedures, NSAIDs are sometimes withheld during the first 24 h. See also section 5.1 on the general management of postoperative pain, and section 5.10.1 for the management of craniotomy and major neurosurgery.

Good practice point

Analgesia following neurosurgery requires good communication and close co-operation between members of the peri-operative team. Frequent pain assessments should be a routine part of postoperative care. A multi-modal analgesic approach is suitable, which may include the use of LA infiltration, paracetamol, NSAID (when not contraindicated), and parenteral or oral opioid as determined by assessed analgesic requirements.

5.10.1 Craniotomy and major neurosurgery

Craniotomy is most frequently performed for tumor surgery, repair of vascular anomalies and surgery for epilepsy. Posterior fossa craniotomy, a relatively invasive approach, is more frequently indicated in children than adults yet in common with other pediatric neurosurgical procedures postoperative pain and analgesia requirements have been little studied.

Evidence

The literature informing the management of postoperative pain after neurosurgery is limited. There have been few studies comparing standard analgesic regimens.

Opioids: the use of parenteral opioids following craniotomy and major neurosurgery has been described (387–390). PCA with fentanyl plus a continuous infusion of midazolam has been described (391). NCA was reportedly used successfully in a small number of patients <6 years old following neurosurgical procedures as part of a large case series, but results for these patients were not reported separately (221,223). The effective use of codeine has also been described (388,389), in a pharmacokinetic study comparing IM and PR codeine following craniotomy high pain scores were reported for both groups (392).

Analgesia Table 5.10.1 Craniotomy and major neurosurgery

Agent	Technique	Direct evidence	Indirect evidence
LA	Infiltration		1–
Opioid	IV infusion	2–	
Opioid	PCA/NCA	3	
Opioid (Codeine)	Intramuscular	2–	
Opioid	Intrathecal	2–	
NSAID[a]			1+
Paracetamol[a]			1+

[a]As part of a multi-modal technique.

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Section 6.0

Analgesia

Contents

6.1 Analgesia

This section describes some of the important properties, dosing regimens, interactions, and adverse effects of analgesics for acute pain in children.

Local anesthetics, opioids, NSAIDs, and paracetamol form the pharmacological basis for the majority of analgesic regimens. Ketamine, a dissociative anesthetic with analgesic properties and clonidine, an alpha-2-agonist, are used to provide systemic or neuraxial analgesia alone or as adjuncts to other agents. For painful procedures, inhaled nitrous oxide has an important role, and in neonatology intra-oral sucrose solution is used. The availability of specific opioids, NSAIDs, and local anesthetics can vary from country to country.

The detailed pharmacology and formulations of these drugs are available in standard textbooks. For more comprehensive prescribing information, summaries of product characteristics, and license status of specific agents for children in the UK, please consult resources such as the British National Formulary for Children (2012) available at http://bnfc.org/bnfc and the Electronic Medicines Compendium available at http://emc.medicines.org.uk/.

6.2 Local anesthetics

Most widely used local anesthetics are amides with the exception of tetracaine (amethocaine), which is an ester (1–4). They all act by reversibly blocking sodium channels in nerves. They vary in onset, potency, potential for toxicity, and duration of effect. Formulations are available for topical application to mucosae or intact skin, for local installation or infiltration, for peripheral nerve or plexus blockade, for epidural injection or infusion, and for subarachnoid administration. Vasoconstrictors may be added to reduce the systemic absorption of local anesthetic and to prolong the neural blockade. Neuraxial analgesics such as the α-2-agonist clonidine, the phencyclidine derivative ketamine, or opioids such as fentanyl may be co-administered with the local anesthetic to prolong the effect of central nerve blocks.

6.2.1 Bupivacaine, levobupivacaine, and ropivacaine

(i) Preparations and routes

Bupivacaine is an amide LA with a slow onset and a long duration of action, which may be prolonged by the addition of a vasoconstrictor. It is used mainly for infiltration anesthesia and regional nerve blocks, particularly epidural block, but is contraindicated for intravenous regional anesthesia (Bier's block). Bupivacaine is a racemic mixture but the S(−)-isomer levobupivacaine is also commonly used. A carbonated solution of bupivacaine, with faster onset of action, is also available for injection in some countries. Bupivacaine is used in solutions containing the equivalent of

0.0625–0.75% (0.625–7.5 mg ml^{-1}). In recommended doses, bupivacaine produces complete sensory blockade, and the extent of motor blockade depends on concentration. Solutions of 0.0625% or 0.125% are associated with a very low incidence of motor block, a 0.25% solution generally produces incomplete motor block, a 0.5% solution will usually produce more extensive motor block, and complete motor block and muscle relaxation can be achieved with a 0.75% solution. Hyperbaric solutions of 0.5% bupivacaine may be used for spinal intrathecal block.

Levobupivacaine is the S-enantiomer of bupivacaine, and it is equipotent but toxicity is slightly less. It is available in the same concentrations as bupivacaine and is used for similar indications; like bupivacaine, it is contraindicated for use in intravenous regional anesthesia (Bier's block).

Ropivacaine is an amide LA with an onset and duration of sensory block that is generally similar to that obtained with bupivacaine but motor block may be slower in onset, shorter in duration, and less intense. It is available in solutions of 0.2%, 0.75%, and 1%.

(ii) Dosage, side effects, and toxicity

The dosage of *bupivacaine, levobupivacaine,* and *ropivacaine* depends on the site of injection, the procedure, and the status of the patient: suggested maxima are given in Table 6.2.1. A test dose may help to detect inadvertent intravascular injection, and doses should be given in small increments. Slow accumulation occurs with repeat administration and continuous infusions, especially in neonates.

Table 6.2.1 Suggested maximum dosages of bupivacaine, levobupivacaine, and ropivacaine

Single bolus injection	Maximum dosage ($mg \cdot kg^{-1}$)
Neonates	2
Children	2.5
Continuous infusion (postoperative use)	Maximum infusion rate ($mg \cdot kg^{-1} \cdot h^{-1}$)
Neonates	0.2
Children	0.4

Bupivacaine is 95% bound to plasma proteins with a half-life of 1.5–5.5 h in adults and 8 h in neonates. It is metabolized in the liver and is excreted in the urine mainly as metabolites with only 5–6% as unchanged drug. Bupivacaine is distributed into breast milk in small quantities. It crosses the placenta but the ratio of fetal concentrations to maternal concentrations is relatively low. Bupivacaine also diffuses into the CSF.

The toxic threshold for bupivacaine is in the plasma concentration range of 2–4 $mg \cdot ml^{-1}$. The two major binding proteins for bupivacaine in the blood are α1-acid glycoprotein, the influence of which is predominant at low concentrations, and albumin, which plays the major role at high concentrations. Reduction in pH from 7.4 to 7.0 decreases the affinity of the α1-acid glycoprotein for bupivacaine but has no effect on albumin affinity. For epidural infusion techniques in neonates, the reduced hepatic clearance of amide local anesthetics is the more important factor causing accumulation of bupivacaine than reduced protein binding capacity, particularly as protein levels tend to increase in response to surgery.

Bupivacaine is more cardio toxic than other amide local anesthetics and there is an increased risk of myocardial depression in overdose and when bupivacaine and antiarrhythmics are given together. Propranolol reduces the clearance of bupivacaine. *Levobupivacaine* is slightly less cardio toxic and therefore safer but maximum recommended doses are similar to those of buivacaine.

Ropivacaine is about 94% bound to plasma proteins. The terminal elimination half-life is around 1.8 h, and it is extensively metabolized in the liver by the cytochrome P450 isoenzyme CYP1A2. Prolonged use of ropivacaine should be avoided in patients treated with potent CYP1A2 inhibitors, such as the selective serotonin reuptake inhibitor (SSRI) fluvoxamine. Plasma concentrations of ropivacaine may be reduced by enzyme-inducing drugs such as rifampicin. Metabolites are excreted mainly in the urine; about 1% of a dose is excreted as unchanged drug. Some metabolites also have a local anesthetic effect but less than that of ropivacaine. Ropivacaine crosses the placenta.

6.2.2 Lidocaine, prilocaine, and EMLA

(i) Preparations

Lidocaine is an amide LA, which is used for infiltration anesthesia and regional nerve blocks. It has a rapid onset of action and anesthesia is obtained within a few minutes; it has an intermediate duration of action. The addition of a vasoconstrictor reduces systemic absorption and increases both the speed of onset and the duration of action. Lidocaine is a useful surface anesthetic but it may be rapidly and extensively absorbed following topical application to mucous membranes, and systemic effects may occur. Hyaluronidase may

enhance systemic absorption. Lidocaine is included in some injections, such as depot corticosteroids, to prevent pain and itching caused by local irritation.

Prilocaine is an amide local anesthetic with a similar potency to lidocaine. However, it has a slower onset of action, less vasodilator activity, and a slightly longer duration of action; it is also less toxic. Prilocaine is used for infiltration anesthesia and nerve blocks in solutions of 0.5%, 1%, and 2%. A 1% or 2% solution is used for epidural anesthesia; for intravenous regional anesthesia, 0.5% solutions are used. For dental procedures, a 3% solution with the vasoconstrictor felypressin or a 4% solution without is used. A 4% solution with epinephrine (1 in 200 000) is also used for dentistry in some countries. Carbonated solutions of prilocaine have also been used for epidural and brachial plexus nerve blocks. Prilocaine is used for surface anesthesia in a eutectic mixture with lidocaine *EMLA*.

(ii) Doses, side effects, and toxicity

The dose of *lidocaine* depends on the site of injection and the procedure but in general, the maximum dose should not exceed 3 $mg \cdot kg^{-1}$ (maximum 200 mg) unless vasoconstrictor is also used. Lidocaine hydrochloride solutions containing epinephrine (1 in 200 000) for infiltration anesthesia and nerve blocks are available; higher concentrations of epinephrine are seldom necessary, except in dentistry, where solutions of lidocaine hydrochloride with epinephrine 1 in 80 000 are traditionally used. The maximum dose of epinephrine should be 5 microgm/kg^{-1} and of lidocaine 5 $mg \cdot kg^{-1}$. Epinephrine-containing solutions should not be used near extremities such as for digital or penile blocks. Lidocaine may be used in a variety of formulations for surface anesthesia. Lidocaine ointment is used for anesthesia of skin and mucous membranes. Gels are used for anesthesia of the urinary tract and for analgesia of aphthous ulcers. Topical solutions are used for surface anesthesia of mucous membranes of the mouth, throat, and upper gastrointestinal tract. For painful conditions of the mouth and throat, a 2% solution may be used or a 10% spray can be applied to mucous membranes. Eye drops containing lidocaine hydrochloride 4% with fluorescein are used in tonometry. Other methods of dermal delivery include a transdermal patch of lidocaine 5% for the treatment of pain associated with postherpetic neuralgia and an iontophoretic drug delivery system incorporating lidocaine and epinephrine.

Lidocaine is bound to plasma proteins, including α1-acid glycoprotein (AAG). The extent of binding is variable but is about 66%. Plasma protein binding of lidocaine depends in part on the concentrations of both lidocaine and AAG. Any alteration in the concentration of AAG can greatly affect plasma concentrations of lidocaine. Plasma concentrations decline rapidly after an intravenous dose with an initial half-life of < 30 min; the elimination half-life is 1–2 h but may be prolonged if infusions are given for longer than 24 h or if hepatic blood flow is reduced. Lidocaine is largely metabolized in the liver, and any alteration in liver function or hepatic blood flow can have a significant effect on its pharmacokinetics and dosage requirements. First-pass metabolism is extensive and bioavailability is about 35% after oral doses. Metabolism in the liver is rapid and about 90% of a given dose is dealkylated to form monoethylglycinexylidide and glycinexylidide. Both of these metabolites may contribute to the therapeutic and toxic effects of lidocaine and because their half-lives are longer than that of lidocaine, accumulation, particularly of glycinexylidide, may occur during prolonged infusions. Further metabolism occurs and metabolites are excreted in the urine with $< 10\%$ of unchanged lidocaine. Reduced clearance of lidocaine has been found in patients with heart failure or severe liver disease. Drugs that alter hepatic blood flow or induce drug-metabolizing microsomal enzymes can also affect the clearance of lidocaine. Renal impairment does not affect the clearance of lidocaine but accumulation of its active metabolites can occur. Lidocaine crosses the placenta and blood–brain barrier; it is distributed into breast milk. Lidocaine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals.

The clearance of lidocaine may be reduced by propranolol and cimetidine. The cardiac depressant effects of lidocaine are additive with those of beta blockers and of other antiarrhythmics. Additive cardiac effects may also occur when lidocaine is given with intravenous phenytoin, mexilitene, or amiodarone; however, the long-term use of phenytoin and other enzyme inducers such as barbiturates may increase dosage requirements of lidocaine. Hypokalaemia produced by acetazolamide, loop diuretics, and thiazides antagonizes the effect of lidocaine.

Prilocaine dosage for children over 6 months of age is up to 5 $mg \cdot kg^{-1}$. For dental infiltration or dental nerve blocks, the 4% solution with epinephrine (1:200 000) is often used. Children under 10 years generally require about 40 mg (1 ml). The dose of prilocaine hydrochloride with felypressin 0.03 international $units \cdot ml^{-1}$ as a 3% solution for children under 10 years is 30–60 mg (1–2 ml).

Prilocaine has relatively low toxicity compared with most amide-type local anesthetics. It is 55% bound to plasma proteins and is rapidly metabolized mainly in the liver and kidneys and is excreted in the urine. One of the principal metabolites is o-toluidine, which is believed to cause the methemoglobinemia observed after large doses. It crosses the placenta and during prolonged epidural anesthesia may produce methemoglobinemia in the fetus. It is distributed into breast milk. The peak serum concentration of prilocaine associated with CNS toxicity is 20 $mg \cdot ml^{-1}$. Symptoms usually occur when doses of prilocaine hydrochloride exceed about 8 $mg \cdot kg^{-1}$ but the very young may be more susceptible. Methemoglobinemia has been observed in neonates whose mothers received prilocaine shortly before delivery and it has also been reported after prolonged topical application of a prilocaine/lidocaine eutectic mixture in children. Methemoglobinemia may be treated by giving oxygen followed, if necessary, by IV methylthioninium chloride.

Prilocaine should be used with caution in patients with anemia, congenital or acquired methemoglobinemia, cardiac or ventilatory failure, or hypoxia. Prilocaine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients. Methemoglobinemia may occur at lower doses of prilocaine in patients receiving therapy with other drugs known to cause such conditions (e.g., sulfonamides such as sulfamethoxazole in co-trimoxazole).

(iii) EMLA

Lidocaine forms a mixture with prilocaine that has a melting point lower than that of either ingredient. This eutectic mixture containing lidocaine 2.5% and prilocaine 2.5% can produce local anesthesia when applied to intact skin as a cream. It is used extensively for procedural pain including venepuncture, intravenous or arterial cannulation, lumbar puncture, minor dermatological procedures, and others (see section 4.0). The eutectic cream is usually applied to skin under an occlusive dressing for at least 60 min and a maximum of 5 h. Transient paleness, redness, and edema of the skin may occur following application.

Eutectic mixtures of lidocaine and prilocaine are used in neonates and are safe in single doses. There has been concern that excessive absorption (particularly of prilocaine) might lead to methemoglobinemia particularly after multiple applications. For this reason, the maximum number of doses per day should be limited in the neonate. In some countries, EMLA has been licensed for use in neonates provided that their gestational age is at least 37 weeks, and that methemoglobin values are monitored in those aged 3 months or less. In fact, systemic absorption of both drugs from the eutectic cream appears to be minimal across intact skin even after prolonged or extensive use. However, EMLA should not be used in infants under 1 year who are receiving methemoglobin-inducing drugs; it should not be used on wounds or mucous membranes or for atopic dermatitis. EMLA should not be applied to or near the eyes because it causes corneal irritation, and it should not be instilled into the middle ear. It should be used with caution in patients with anemia or congenital or acquired methemoglobinemia.

6.2.3 Tetracaine (amethocaine)

(i) Preparations

Tetracaine is a potent, para-aminobenzoic acid ester local anesthetic used for surface anesthesia and spinal block. It is highly lipophilic and can penetrate intact skin. Its use in other local anesthetic techniques is restricted by its systemic toxicity.

For anesthesia of the eye, solutions containing 0.5–1% tetracaine hydrochloride and ointments containing 0.5% tetracaine have been used. Instillation of a 0.5% solution produces anesthesia within 25 s that lasts for 15 min or longer and is suitable for use before minor surgical procedures.

A 4% gel (Ametop) is used as a percutaneous local anesthetic. This formulation of 4% tetracaine produces more rapid and prolonged surface anesthesia than EMLA and is significantly better in reducing pain caused by laser treatment of port wine stains and for venous cannulation. A transdermal patch is effective, and patches containing a mixture of lidocaine and tetracaine have also been tried. Tetracaine has been incorporated into a mucosa-adhesive polymer film to relieve the pain of oral lesions resulting from radiation and antineoplastic therapy. Liposome-encapsulated tetracaine can provide adequate surface anesthesia.

LAT (LET) 4% lidocaine, 0.1% epinephrine, and 0.5% tetracaine have been combined in a gel and applied as a surface anesthetic to lacerations of the skin especially the face and scalp. It is less a painful alternative to LA infiltration prior to suture of lacerations.

(ii) Dosage side effects and toxicity

Tetracaine: A stinging sensation may occur when tetracaine is used in the eye. Absorption of tetracaine from mucous membranes is rapid, and adverse reactions can

occur abruptly without the appearance of prodromal signs or convulsions; systemic toxicity is high and fatalities have occurred. It should not be applied to inflamed, traumatized, or highly vascular surfaces and should not be used to provide anesthesia for bronchoscopy or cystoscopy, as there are safer alternatives, such as lidocaine.

Tetracaine gel: The gel is applied to the center of the area to be anesthetized and covered with an occlusive dressing. Gel and dressing are removed after 30 min for venepuncture and 45 min for venous cannulation. A single application provides anesthesia for 4–6 h. Tetracaine is 15% bioavailable after application of 4% gel to intact skin, with a mean absorption and elimination half-life of about 75 min. It is rapidly metabolized by esterases in the skin, in plasma, and on red cells. Mild erythema at the site of application is frequently seen with topical use; slight edema or pruritus occur less commonly and blistering of the skin may occur. It has been used safely in the premature neonate from 28 weeks gestation.

LAT: 1–3 ml of the solution is applied directly to the wound for 15–30 min using a cotton-tipped applicator. The solution and gel have been used in children aged 1-year old and above. There are no reports of toxicity but application of preparations of tetracaine to highly vascular surfaces, mucous membranes, and wounds larger than 6 cm is not recommended. If lidocaine is injected following LAT, the maximum dose of lidocaine (5 $mg \cdot kg^{-1}$) should not be exceeded.

6.3 Neuraxial analgesic drugs

Drugs that produce a specific spinally mediated analgesic effect following epidural or intrathecal administration are referred to as neuraxial analgesic drugs (other terms include spinal adjuvants, caudal additives) (5–9). Analgesia is not mediated by systemic absorption of the drug as spinal dose requirements, and associated plasma concentrations are lower than those required for an analgesic effect following systemic administration. These agents modulate pain transmission in the spinal cord by:

- reducing excitation, for example, ketamine (NMDA antagonist)
- enhancing inhibition, for example, opioids; clonidine (alpha2 agonist); neostigmine (anticholinesterase); midazolam ($GABA_A$ agonist)

In pediatric practice, these drugs are most commonly administered as single-dose caudal injections and are often used in combination with local anesthesia to improve and prolong analgesia, reducing the dose requirement for local anesthetic and thereby unwanted effects such as motor block or urinary retention. There is conflicting data about the ability to produce a selective spinally mediated effect in children. Caudal administration of tramadol has been reported to produce lower serum concentrations of metabolites but no difference in analgesia when compared with IV administration. Many studies that compare the effect of neuraxial drugs are hampered by poor study design, such as:

- inadequate power and sample size. If the sample size is small, it is difficult to confirm any change in the incidence of side effects, particularly those that are less common.
- insensitive outcome measures. No difference may be found between two active treatments (e.g., LA ± additive; different doses; different routes such as caudal versus systemic) if pain scores and supplemental analgesic requirements are low in both groups. Measures of side effects such as sedation and respiratory depression are often insensitive and not standardized.

The use of ketamine and clonidine is described here: tramadol and other opioids are discussed in section 6.4. Neostigmine and tramadol increase the duration of analgesia when added to caudal local anesthetic, but also increase the probability of postoperative nausea or vomiting.

6.3.1 Ketamine and clonidine

(i) Preparations and pharmacology

Ketamine

Ketamine is an NMDA antagonist that can produce general anesthesia following intramuscular injection or intravenous bolus and/or infusion. Ketamine produces dissociative anesthesia characterized by a trance-like state, amnesia, and marked analgesia which may persist into the recovery period. There is often an increase in muscle tone and the patient's eyes may remain open for all or part of the period of anesthesia; it can also produce unpleasant emergence phenomena, including hallucinations. Ketamine is a racemic mixture, and the S-isomer has approximately twice the analgesic potency of the racemate. Ketamine

undergoes hepatic biotransformation to an active metabolite norketamine and is excreted mainly in the urine as metabolites. Subanesthetic doses of ketamine produce analgesia. Oral administration has been utilized for sedation/premedication. Caudal/epidural administration of ketamine produces analgesia but concern has been expressed regarding potential neurotoxicity.

Clonidine

Clonidine is an alpha2-adrenergic agonist and has sedative, anxiolytic, and analgesic properties. As a result, potential perioperative benefits include use for premedication, reduction in general anesthetic requirements, analgesia, and management of opioid withdrawal symptoms. Clonidine can be given orally, transdermally, intravenously, or epidurally. Clonidine is rapidly absorbed. After oral administration, about 50% is metabolized in the liver, and it is excreted in the urine as unchanged drug and metabolites. Clearance in neonates is about one-third of adult levels. The elimination half-life has been variously reported to range between 6 and 24 h, and extended up to 41 h in patients with renal impairment. Clonidine crosses the placenta and is distributed into breast milk. The hypotensive effect of clonidine may be enhanced by diuretics, other antihypertensives, and drugs that cause hypotension. The sedative effect of clonidine may be enhanced by CNS depressants. Clonidine has been associated with impaired atrioventricular conduction in a few patients, although some of these may have had underlying conduction defects and had previously received digitalis, which may have contributed to their condition.

(ii) Doses

Ketamine

For anesthesia, 2 $mg \cdot kg^{-1}$ given intravenously over 60 s usually produces surgical anesthesia within 30 s of the end of the injection and lasting for 5–10 min.

Addition of ketamine 0.25–0.5 $mg \cdot kg^{-1}$ to caudal local anesthetic (compared with a local anesthetic alone) prolongs the time to first analgesia and reduces postoperative rescue analgesia requirements.

Clonidine

Clonidine is rapidly absorbed after oral administration and doses of 4 $mcg \cdot kg^{-1}$ have been used for premedication. Clonidine has an established role as a spinal adjuvant analgesic in pediatric practice, and clonidine via the intrathecal or caudal/epidural route has a greater effect than the same dose intravenously. Addition of 1–2 $mcg \cdot kg^{-1}$ clonidine to caudal local anesthetic prolongs analgesia and reduces postoperative analgesic requirements, when compared to local anesthetic alone. Sensitivity to side effects (apnea, oxygen desaturation, and bradycardia) is greater in neonates, and cardiovascular and sedative side effects have been reported following doses of 5 $\mu g \cdot kg^{-1}$ caudal clonidine in children. Epidural clonidine 0.08–0.12 $\mu g \cdot kg^{-1} \cdot h^{-1}$ produces dose-dependent analgesia when added to local anesthetic infusion, and higher doses of clonidine alone (0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ preceded by bolus of 2 $\mu g \cdot kg^{-1}$) provide analgesia at rest following abdominal surgery.

(iii) Neuroxicity

Severe complications following pediatric regional techniques are rare, but the incidence is higher in neonates and infants (0.4% vs 0.1% for all regional blocks or 1.1% vs 0.49% for epidural blocks alone). Rates of neurological injury following neuraxial analgesia range from 0.13 to 0.4 per 1000 in large series, with higher rates following epidural catheter techniques than single shot caudals. Issues relating to the potential neurotoxicity of some spinally administered drugs and the ethical use of unlicensed routes of administration have been debated for many years.

General anesthetics with NMDA antagonist and/or GABA agonist activity increase neuronal apoptosis in the developing brain in rodents and primates and have led to a number of clinical studies evaluating neurocognitive outcomes following exposure to general anesthesia in early life. The potential for additional developmentally regulated spinal toxicity has been the impetus for studies assessing histopathology and apoptosis in the spinal cord following intrathecal drugs in neonatal rodent models. Intrathecal bupivacaine produces dense spinal analgesia but does not increase apoptosis in the brain or spinal cord of neonatal and infant rats. Systemically administered opioids have not been associated with increased apoptosis in the brain, and similarly intrathecal morphine did not increase apoptosis or produce histopathology in the neonatal or infant spinal cord.

Ketamine: In adult models, spinal cord toxicity has been demonstrated following intrathecal administration of ketamine in adult swine, rabbits, and dogs. Although some studies have attributed changes to the preservative, administration of preservative-free S-ketamine for 7 days produced necrotizing lesions with cellular

infiltrates in the cord and a 28-day infusion of preservative-free racemic ketamine produced pathologic changes ranging from mild inflammation and demyelination to marked necrosis. Intrathecal administration of preservative-free ketamine in neonatal rats has been shown to increase apotosis and produce persistent changes in sensory threshold in the same dose range as analgesia.

Clonidine: The neurotoxicity of epidural *clonidine* has been more extensively studied. Repeated bolus or extended continuous epidural and intrathecal delivery of clonidine in adult dogs or rats did not result in toxicity. Similarly, maximal tolerated doses of intrathecal clonidine (300 times analgesic dose) did not increase apoptosis, produce histopathology in the spinal cord, or produce persistent changes in sensory thresholds.

Table 6.3.1 Typical doses of epidural neuraxial analgesics

Drug	Single dose microgm.kg^{-1}	Infusion microgm.kg^{-1}.hr^{-1}	Side effects
Clondine	1–2	0.08–0.2	Sedation; dose related hypotension and bradycardia (5 mcg·kg^{-1}); delayed respiratory depression and bradycardia in neonates
Ketamine	250–500		Hallucinations at higher doses
Morphine	15–50	0.2–0.4	Nausea and vomiting; urinary retention; pruritis; delayed respiratory depression
Fentanyl	0.5–1	0.3–0.8	Nausea and vomiting
Tramadol	500–2000		Nausea and vomiting

6.4 Opioids

Opioids remain the most powerful and widely used group of analgesics. They can be given by many routes of administration and are considered safe, provided accepted dosing regimens are used and appropriate monitoring and staff education are in place. Morphine is the prototype opioid, and diamorphine, tramadol, oxycodone, and hydromorphone are alternatives to morphine in the postoperative period. Fentanyl, sufentanil, alfentanil, and remifentanil have a role during and after major surgery and in intensive care practice and can be used to ameliorate the stress response to surgery. Codeine and dihydrocodeine can be used for short-term treatment of moderate pain. Pethidine (meperidine) is not recommended in children owing to the adverse effects of its main metabolite, nor-pethidine. Opioid infusions can provide adequate analgesia with an acceptable level of side effects. Patient-controlled opioid analgesia is now widely used in children as young as age 5 years and compares favorably with continuous morphine infusion in the older child. NCA where a nurse is allowed to press the demand button within strictly set guidelines can provide flexible analgesia for children who are too young or unable to use PCA. This technology can also be used in neonates where a bolus dose without a background infusion allows the nurse to titrate the child to analgesia or to anticipate painful episodes while producing a prolonged effect because of the slower clearance of morphine. Neuraxial administration of opioids has a place where extensive analgesia is needed, for example, after major abdominal surgery, spinal surgery, or when adequate spread of epidural local anesthetic blockade cannot be achieved within dosage limits.

Table 6.4.1 Opioid potency relative to morphine

Drug	Relative potency	Single dose (oral) mg/kg	Continuous infusion (IV) micrograms.kg^{-1}.hr^{-1}
Tramadol	0.1	1–2	100–400
Codeine	0.1–0.12	0.5–1	N/A
Morphine	1	0.2–0.4	10–40
Hydromorphone	5	0.04–0.08	2–8
Fentanyl	50–100	N/A	0.1–0.2 mg·kg^{-1}·min^{-1} or use TCI[a] system
Remifentanil	50–100	N/A	0.05–4 mcg·kg^{-1}·min^{-1} or use TCI[a] system

[a]Target controlled infusion.

6.4.1 Opioid preparations, dosages, and routes

Morphine

Morphine is the most widely used and studied opioid in children. Its agonist activity is mainly at μ opioid receptors (10,11). It can be given by the oral, subcutaneous, intramuscular, intravenous, epidural, intraspinal, and rectal routes. Parenteral administration may be intermittent injection; continuous or intermittent infusion of the dose is adjusted according to individual analgesic requirements. Using accepted dosing regimens, morphine has been shown to be safe and effective in children of all ages.

The pharmacokinetics of morphine in children is generally considered similar to those in adults but in neonates and into early infancy the clearance and pro-

tein binding are reduced and the half-life is increased. These differences, which are dependent on gestational age and birth weight, are mainly due to reduced metabolism and immature renal function in the developing child. This younger age group demonstrates an enhanced susceptibility to the effects, and the side effects of morphine and dosing schedules must be altered to take this into account. Morphine has poor oral bioavailability as it undergoes extensive first-pass metabolism in the liver and gut.

Morphine dosing schedules

An appropriate monitoring protocol should be used dependent on the route of administration and age of the child. For neuraxial dosing, see section 6.2.
Oral:
Neonate: 80 mcg·kg^{-1} 4–6 hourly
Child: 200–500 mcg·kg^{-1} 4 hourly

Intravenous or subcutaneous loading dose: (titrated according to response)
Neonate: 25 mcg·kg^{-1} increments
Child: 50 mcg·kg^{-1} increments

Intravenous or subcutaneous infusion:
10–40 mcg·kg^{-1}·h^{-1}

Patient-controlled analgesia (PCA):
Bolus (demand) dose: 10–20 mcg·kg^{-1}
Lockout interval: 5–10 min
Background infusion: 0–4 mcg·kg^{-1}·h^{-1}

Nurse controlled analgesia (NCA):
Bolus (demand) dose: 10–20 mcg·kg^{-1}
Lockout interval: 20–30 min
Background infusion: 0–20 mcg·kg^{-1}·h (<5 kg use no background)

Diamorphine

Diamorphine hydrochloride is an acetylated morphine derivative and is a more potent opioid analgesic than morphine. It is much more lipid soluble and has a more rapid onset and shorter duration of action than morphine. Diamorphine can be given by the oral, intranasal, subcutaneous, intramuscular, intravenous, and epidural and intrathecal routes. Because of its abuse potential, the supply of diamorphine is carefully controlled and in many countries it is not available for clinical use.

On injection, diamorphine is rapidly converted to the active metabolite 6-O-monoacetylmorphine (6-acetylmorphine) in the blood and then to morphine. Oral doses are subject to extensive first-pass metabolism to morphine. As with morphine, neonates and infants have altered pharmacokinetics and an increased susceptibility to the opioid effects of diamorphine.

Diamorphine dosing schedules

An appropriate monitoring protocol should be used dependent on the route of administration and age of the child.
Oral: >1 year 100–200 mcg·kg^{-1} 4 hourly

Intravenous or subcutaneous loading dose: (titrated according to response)
Neonate: 10–25 mcg·kg^{-1} increments
Child: 25–100 mcg·kg^{-1} increments

Intravenous or subcutaneous infusion:
2.5–25 mcg·kg^{-1}·h^{-1}

Intranasal:
100 mcg·kg^{-1} in 0.2 ml sterile water instilled into one nostril.

Hydromorphone

Hydromorphone is an opioid analgesic related to morphine but with a greater analgesic potency and is used for the relief of moderate-to-severe pain. It is a useful alternative to morphine for subcutaneous use because its greater solubility in water allows a smaller dose volume.

Hydromorphone dosing schedules

Oral: 40–80 microg/kg 4 hourly

Intravenous or subcutaneous loading dose: (titrated according to response)
Child <50 kg: 10–20 microg/kg increments

Intravenous or subcutaneous infusion: 2-8 microg/kg/h·kg^{-1}·h^{-1}

Codeine

Codeine is much less efficacious than morphine and is used for the relief of mild-to-moderate pain. It is often given in combination with NSAIDs or paracetamol. Codeine can also be given by intramuscular injection, in doses similar to those by mouth; the intravenous route should not be used as severe hypotension may occur.

The analgesic effect of codeine is unpredictable. Its effects may be wholly or mainly due to metabolism to morphine. The enzyme responsible for this conversion, CYP2D6, shows significant genetic variation and across populations the amount of codeine converted to morphine is very variable. Development may also affect CYP2D6 activity with lower levels of activity found in neonates and infants.

Codeine dosing schedules

Oral, intramuscular or rectal:

Neonate or child: 0.5–1 $mg \cdot kg^{-1}$ 4–6 hourly (care with repeated doses in neonates)

Dihydrocodeine

Dihydrocodeine is an opioid analgesic related to codeine. It is used for the relief of moderate-to-severe pain, often in combination with paracetamol. The analgesic effect of dihydrocodeine appears to be primarily due to the parent compound (unlike codeine); it is metabolized in the liver via the cytochrome P450 isoenzyme CYP2D6 to dihydromorphine, which has potent analgesic activity, and some is also converted via CYP3A4 to nordihydrocodeine.

Dihydrocodeine dosing schedules

Oral or intramuscular:

>1 year: 0.5–1 $mg \cdot kg^{-1}$ 4–6 hourly

Oxycodone

Oxycodone can be given by mouth or by subcutaneous or intravenous injection for the relief of moderate-to-severe pain (12). It can be given by continuous infusion or PCA. The oral potency is about twice that of morphine, whereas intravenously it is about 1.5 times as potent. Although not widely used at present in the United Kingdom, it may be a useful and safe alternative to morphine and codeine as an oral opioid.

Oxycodone dosing schedules

Oral: 100–200 $mg \cdot kg^{-1}$ 4–6 hourly

Tramadol

Tramadol hydrochloride is an opioid analgesic with noradrenergic and serotonergic properties that may contribute to its analgesic activity (13,14). Tramadol can be given by mouth, intravenously, or as a rectal suppository. It has also been given by infusion or as part of a PCA system.

Tramadol is increasingly used in children of all ages and has been shown to be effective against mild-to-moderate pain. It may produce fewer typical opioid adverse effects such as respiratory depression, sedation, and constipation; though, it demonstrates a relatively high rate of nausea and vomiting.

Tramadol dosing schedules:

Oral, rectal, or intravenous: 1–2 $mg \cdot kg^{-1}$ 4–6 hourly

Fentanyl

Fentanyl is a potent opioid analgesic related to pethidine and is primarily a μ-opioid agonist. It is more lipid soluble than morphine and it has a rapid onset and short duration of action. Because of its high lipophilicity, fentanyl can also be delivered via the transdermal (±iontophoresis) or transmucosal routes. Small intravenous bolus doses can be injected immediately after surgery for postoperative analgesia and PCA systems have been used.

After transmucosal delivery, about 25% of the dose is rapidly absorbed from the buccal mucosa; the remaining 75% is swallowed and slowly absorbed from the gastrointestinal tract. Some first-pass metabolism occurs via this route. The absolute bioavailability of transmucosal delivery is 50% of that for intravenous fentanyl. Absorption is slow after transdermal application.

The clearance is decreased and the half-life of fentanyl is prolonged in neonates. As with morphine, neonates are more susceptible to the adverse effects of fentanyl, and appropriate monitoring and safety protocols should be implemented when fentanyl is used in this age group. There are differences in pharmacokinetics between bolus doses and prolonged infusion with highly lipophilic drugs such as fentanyl; the context-sensitive half-time progressively increases with the duration of infusion.

Fentanyl dosing schedules

An appropriate monitoring protocol should be used dependent on the route of administration and age of the child. For neuraxial dosing, see section 6.3.

Intravenous dose: titrated according to response

0.5–1.0 $mcg \cdot kg^{-1}$ (decrease in neonates)

Intravenous infusion: 0.5–2.5 $mcg \cdot kg^{-1} \cdot h^{-1}$

Transdermal: 12.5–100 $mcg \cdot h^{-1}$

Remifentanil

Remifentanil is a potent short-acting μ-receptor opioid agonist used for analgesia during induction and/or maintenance of general anesthesia. It has also been used to provide analgesia into the immediate postoperative period. Remifentanil is given intravenously, usually by infusion. Its onset of action is within 1 min and the duration of action is 5–10 min. Remifentanil is metabolized by esterases and so its half-life is independent of the dose, duration of infusion, and age of child.

Remifantanil is a strong respiratory depressant. It can be used in the spontaneously breathing patient as

a low-dose infusion but the child must be nursed in an appropriate area with adequate monitoring. When appropriate, alternative analgesics should be given before stopping remifentanil, in sufficient time to provide continuous and more prolonged pain relief.

6.4.2 Opioid toxicity and side effects

Opioids have a wide range of effects on a number of different organ systems (See Table 6.4.2). These provide not only clinically desirable analgesic effects but also the wide range of adverse effects associated with opioid use.

The profile of side effects is not uniform between the opioids or even between patients taking the same opioid. The incidence and severity of side effects in an individual patient are influenced by a number of genetic and developmental factors and therefore appropriate monitoring and adverse effect management should be performed with the use of opioids.

Table 6.4.2 Physiological effects of opioids

Central nervous system
Analgesia
Sedation
Dysphoria and euphoria
Nausea and vomiting
Miosis
Seizures
Pruritis
Psychomimetic behaviors, excitation
Respiratory system
Antitussive
Respiratory depression
↓ respiratory rate
↓ tidal volume
↓ ventilatory response to carbon dioxide
Cardiovascular system
Minimal effects on cardiac output
Heart rate
Bradycardia seen on most occasions
Vasodilation, venodilation
Morphine other opioids ? histamine effect
Gastrointestinal system
↓ intestinal motility and peristalsis
↑ sphincter tone
Sphincter of oddi
Ileocolic
Urinary system
↑ Tone
Uterus
Bladder
Detrusor muscles of the bladder
Musculoskeletal system
↑ chest wall rigidity

6.5 Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are effective for the treatment of mild or moderate pain in children. In addition to analgesia, they have anti-inflammatory and antipyretic effects. They are opioid sparing. The combination of NSAIDs and paracetamol produces better analgesia than either drug alone. Their mechanism of action is the inhibition of cyclooxygenase (COX) activity, thereby blocking the synthesis of prostaglandins and thromboxane. Aspirin, a related compound, is not used in children because of the potential to cause Reye's syndrome.

6.5.1 NSAID preparations, dose, and routes

A number of convenient NSAID formulations are available:

- Ibuprofen tablet and syrup formulations for oral administration and a dispersible tablet for sublingual administration
- Diclofenac tablet (dispersible and enteric coated), suppository and parenteral formulations
- Ketorolac for intravenous use
- Naproxen oral tablets
- Piroxicam oral tablets and a dispersible sublingual formulation
- Ketoprofen oral tablets and syrup, parenteral formulations

Selective COX 2 inhibitors have been developed with the expectation that the analgesic and anti-inflammatory effects of NSAIDs would be retained while reducing the risk of gastric irritation and bleeding. However, in adult studies potential improvements in safety have been offset by an increase in the incidence of adverse cerebral and cardiac thrombotic events. Reports of the use of selective COX-2 inhibitors in children are appearing in the literature, which demonstrate equal efficacy with nonselective NSAIDs. However, their role in pediatric practice is yet to be established. Pharmacokinetic data for the neonatal use of ibuprofen have been established from its use in patent ductus arteriosus closure. Clearance is reduced and the volume of distribution is increased. However, its use as an analgesic below age 3 months is not recommended, see section 6.5.3.

Table 6.5.1

NSAID	Dose $mg \cdot kg^{-1}$	Interval hours	Maximum daily dose $mg \cdot kg^{-1} \cdot day^{-1}$	Licensed from age
Ibuprofen	5–10	6–8	30	3 months
Diclofenac	1	8	3	6 months
Ketorolac[a]	0.5	6	2	
Naproxen	7.5	12	15	
Piroxicam[a]	0.5	24	0.5	N/R
Ketoprofen[a]	1	6	4	

[a]High incidence of GI complications. Not licensed for acute pain.

6.5.2 NSAID toxicity and side effects

Because of their mechanism of action, NSAIDs have the potential to cause adverse effects at therapeutic plasma levels.

- Hypersensitivity reactions

- NSAIDs reduce platelet aggregation and prolong bleeding time. Therefore, they are usually contraindicated in children with coagulation disorders or in those who are receiving anticoagulant therapy.

- NSAIDs can inhibit prostaglandin-mediated renal function, and this effect is greater in the presence of renal disease and dehydration. Ibuprofen has been shown to reduce the glomerular filtration rate in neonates by 20%. NSAIDs should not be administered concurrently with nephrotoxic agents. Renal toxicity is low in healthy children.

- NSAIDs can cause gastric irritation and bleeding. They are therefore relatively contraindicated in children with a history of peptic ulcer disease. Ibuprofen has the lowest potential for gastric irritation. The risk of adverse GI effects is low when NSAID use is limited to 1–3 days in the postoperative period; it may be further reduced by co-prescription of proton pump inhibitors, for example, omeprazole and H2 antagonists in patients at higher risk. Piroxicam, ketorolac, and ketoprofen are known to be especially likely to cause GI side effects particularly in the elderly. In the UK, piroxicam is no longer licensed for acute indications and is subject to special prescribing and monitoring restrictions.

- Owing to excess leukotriene production, NSAIDs have the potential to exacerbate *asthma* in a predisposed subset of asthmatics. It is estimated that 2% of asthmatic children are susceptible to aspirin-induced bronchospasm and 5% of this subgroup are likely to be cross-sensitive to other NSAIDs, that is, 1:1000. The incidence of asthma in children is increasing, and it is important that children who are not sensitive are not denied the benefits of NSAIDs. History of previous uneventful NSAID exposure should be established in asthmatic children whenever possible. Studies have provided some reassuring data regarding the safety of short-term use of ibuprofen and diclofenac in asthmatic children. NSAIDs should be avoided in children with severe acute asthma.

- NSAIDs should be used with caution in children with severe eczema, multiple allergies, and in those with nasal polyps. NSAIDs should be avoided in liver failure

- Animal studies using high doses of Ketorolac demonstrated delayed bone fusion. This has led to concern that the use of NSAIDs in children may delay bone healing following fracture or surgery. This has not been supported by human studies, and the analgesic benefits of short-term NSAID use outweigh the hypothetical risk of delayed bone healing: see section 5.8.

- NSAIDs are not currently recommended for analgesia in neonates due to concerns that they may adversely affect cerebral and pulmonary blood flow regulation.

Of the NSAIDs currently available, ibuprofen has the fewest side effects and the greatest evidence to support its safe use in children. In a large community-based study in children with fever, the risk of hospitalization for GI bleeding, renal failure, and anaphylaxis was no greater for children given ibuprofen than those given paracetamol (15).

6.6 Paracetamol

Paracetamol is a weak analgesic (16,17). On its own, it can be used to treat mild pain; in combination with NSAIDs or a weak opioid such as codeine, it can be used to treat moderate pain. Studies have demonstrated an opioid sparing effect when it is administered postoperatively.

6.6.1 Paracetamol preparations, doses, and routes

Paracetamol is available for oral administration in syrup, tablet, and dispersible forms. Following oral administration, maximum serum concentrations are reached in 30–60 min. As the mechanism of action is central, there is a further delay before maximum analgesia is achieved. Suppositories are available; however, there is wide variation in the bioavailability of paracetamol following rectal administration. Studies have demonstrated the need for higher loading doses (of the

Table 6.6.1 Paracetamol dosing guide – oral and rectal administration

Age	Route	Loading dose ($mg \cdot kg^{-1}$)	Maintenance dose ($mg \cdot kg^{-1}$)	Interval (h)	Maximum daily dose ($mg \cdot kg^{-1}$)	Duration at maximum dose (h)
28–32 weeks PCA	Oral	20	10–15	8–12	30	48
	Rectal	20	15	12		
32–52 weeks PCA	Oral	20	10–15	6–8	60	48
	Rectal	30	20	8		
>3 months	Oral	20	15	4	90	48
	Rectal	40	20	6		

PCA, postconceptual age.

Table 6.6.2 IV Paracetamol dosing guide

Weight (kg)	Dose	Interval (h)	Maximum daily dose
<5 (term neonate)	7.5 $mg \cdot kg^{-1}$	4–6	30 $mg \cdot kg^{-1}$
5–10	10 $mg \cdot kg^{-1}$	4–6	40 $mg \cdot kg^{-1}$
10–50	15 $mg \cdot kg^{-1}$	4–6	60 $mg \cdot kg^{-1}$
>50	1 g	4–6	4 g

order of 40 $mg \cdot kg^{-1}$) to achieve target plasma concentrations of 10 $mg \cdot l^{-1}$ following rectal administration. The time to reach maximum serum concentration following rectal administration varies between 1 and 2.5 h. Rectal administration of drugs is contraindicated in neutropenic patients because of the risk of causing sepsis. Recently, an intravenous preparation of paracetamol has become available. Initial experience with IV paracetamol is that the higher effect site concentration achieved following intravenous administration is associated with higher analgesic potency. When administered IV, it should be given as an infusion over 15 min.

There are several published dosage regimens for paracetamol (perhaps indicating that the optimum regimen is still to be determined). The regimen used will depend on the age of the child, the route of administration, and the duration of treatment. The clearance in neonates is reduced and the volume of distribution is increased. The dose of paracetamol therefore needs to be reduced in neonates – see Table 1. Bioavailability following rectal administration is higher in the neonate. The current recommendations stated in the BNFc are shown in Tables 6.6.1 and 6.6.2.

6.6.2 Paracetamol toxicity and side effects

When the maximum daily dose of paracetamol is observed, it is well tolerated. The maximum daily dose is limited by the potential for hepatotoxicity that can occur following overdose (exceeding 150 $mg \cdot kg^{-1}$). Multiple doses may lead to accumulation in children who are malnourished or dehydrated. The mechanism of toxicity in overdosage is the production of *N*-acetyl-*p*-benzoquinoneimine (NABQI). The amount of NABQI produced following therapeutic doses of paracetamol is completely detoxified by conjugation with glutathione. In overdosage, glutathione stores become depleted allowing NABQI to accumulate and damage hepatocytes. Acetylcysteine and methionine replenish stores of glutathione and are therefore used in the treatment of toxicity.

6.7 Nitrous oxide (N_2O)

6.7.1 Preparations, dosage, and administration

Nitrous oxide is supplied compressed in metal cylinders labeled and marked according to national standards (18). It is a weak anesthetic with analgesic properties rapidly absorbed on inhalation. The blood/gas partition coefficient is low, and most of the inhaled N_2O is rapidly eliminated unchanged through the lungs. Premixed cylinders with 50% N_2O in oxygen are available, but it is also occasionally administered at inspired concentrations up to 70% with oxygen.

Nitrous oxide inhalation using a self-administration with a face mask or mouthpiece and 'demand valve' system is widely used for analgesia during procedures such as dressing changes, venepuncture, as an aid to postoperative physiotherapy, and for acute pain in emergency situations, see section 4.0. It is also used in dentistry. The system is only suitable for children able to understand and operate the valve, generally those over 5 years of age. Heathcare workers must be specifically trained in the safe and correct technique of administration of N_2O.

Nitrous oxide is given using a self-administration demand flow system operated by the patient unaided such that sedation leads to cessation of inhalation. Analgesia is usually achieved after 3 or 4 breaths. Recovery is rapid once the gas is discontinued.

Continuous flow techniques of administration, where the facemask is held by a healthcare worker rather than the patient, is capable of producing deep sedation and unconsciousness, and therefore the use of this method is not included in this guideline.

6.7.2 Side effects and toxicity

Nitrous oxide potentiates the CNS depressant effects of other sedative agents. There is a risk of increased

pressure and volume from the diffusion of nitrous oxide into closed air-containing cavities and is therefore contraindicated in the presence of pneumothorax. Frequent side effects include euphoria, disinhibition, dizziness, dry mouth, and disorientation. Nausea and vomiting can occur. Excessive sedation is managed by discontinuation of the gas, oxygen administration, and basic airway management. Prolonged or frequent use may affect folate metabolism leading to megaloblastic changes in the bone marrow, megaloblastic anemia, and peripheral neuropathy. Depression of white cell formation may also occur. Patients who receive N_2O more frequently than twice every 4 days should have regular blood cell examination for megaloblastic changes and neutrophil hypersegmentation.

Exposure to prolonged high concentrations of N_2O has been associated with reduced fertility in men and women. It should only be used in a well-ventilated environment, which should be monitored and maintained below the UK Occupational Exposure Standard for atmospheric levels of N_2O that is < 100 ppm.

6.8 Sucrose

Sucrose solutions reduce many physiological and behavioral indicators of stress and pain in neonates (19,20). The effects of sucrose appear to be directly related to the sweet taste of the solution with very low volumes (0.05–2 ml) in concentrations of 12–24% being effective within 2 min of administration.

6.8.1 Sucrose dosage and administration

Sucrose should be administered in a 24% solution 1–2 min before a painful stimulus and may be repeated during the painful procedure if necessary. It can be given using a pacifier or directly dripped (one drop at a time) onto the tongue using a syringe; the number of applications is decided according to the infant's response. Upper volume limits per procedure have been suggested according to the gestational age in weeks:

27–31	0.5 ml maximum
32–36	1.0 ml maximum
> 37	2.0 ml maximum

Each 'dip' of the pacifier is estimated to be 0.2 ml. The effectiveness of sucrose appears to decrease with age, at present it's use as a primary analgesic should be confined to the neonatal period until further information is available.

6.8.2 Sucrose side effects and toxicity

Coughing, choking, gagging, and transient oxygen desaturations have been reported; when using the syringe method, the solution should be applied carefully to the tongue one drop at a time. There is some evidence that adverse effects of sucrose, including a temporary increase in 'Neurobiologic Risk' score, is more frequent in very premature infants, particularly those < 27 and 28–31 weeks gestational age.

6.9 Nonpharmacological strategies

There is increasing interest in the use of nonpharmacological pain management strategies in acute pain. Skin to skin contact and other forms of tactile stimulation have been shown to be effective for needle related procedural pain in neonates (21,22). There is growing evidence supporting the use of psychological interventions for a variety of acute pain indications. Psychological interventions for acute pain include a wide variety of physiological, behavioral, and cognitive techniques aimed at reducing pain and pain-related distress through the modulation of thoughts, behaviors, and sensory information. Some of the most strongly supported are guided imagery, distraction, and hypnosis (23). Some of the terms most commonly used to describe these techniques are detailed below:

- Behavioral interventions are defined as interventions based on principles of behavioral science as well as learning principles by targeting specific behaviors.
- Cognitive interventions are defined as interventions that involve identifying and altering negative thinking styles related to anxiety about the painful situation, and replacing them with more positive beliefs and attitudes, leading to more adaptive behavior and coping styles.
- Distraction includes cognitive techniques to shift attention away from the pain or specific counter activities (e.g., counting, listening to music, playing videogames, talking about something else other than pain or the medical procedure).
- Hypnosis is a psychological state of heightened awareness and focused attention, in which critical faculties are reduced and susceptibility and receptiveness to ideas is greatly enhanced.
- Psychological preparation refers to specific interventions designed to provide information about the procedure and reduce anxiety. Often three types of information is provided: information about the procedure itself (i.e., steps that children must perform and

steps that health care professionals will perform); the sensations the patient can expect to feel (e.g., sharp scratch, numbness); and about how to cope with the procedure.

- Relaxation is a state of relative freedom from anxiety and skeletal muscle tension, a quieting or calming of the mind and muscles.

Further reading

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