Introduction

Regional anesthesia has wide-ranging benefits but requires technical expertise. Its use in neonates, infants, and children continues to escalate, both as a sole anesthetic or in combination with general anesthesia, to provide both intraoperative and initial postoperative analgesia (1–7). Untreated pain has several deleterious effects, whereas effective pain relief may play a significant role in surgical outcome because ‘untreated’ surgical stress produces a spectrum of autonomic, hormonal, metabolic, immunologic/inflammatory, and neurobehavioral consequences. Regional anesthesia is almost universally employed to provide analgesia, but it may also be used for its autonomic and motor effects in special circumstances.

In choosing regional anesthesia, the risks and benefits of the technique must be weighed against the risks and benefits of other forms of analgesia. Many factors influence the choice of technique (4–7). These include informed consent, the age and general condition of the patient, and the presence of co-morbidities (respiratory, cardiac), the severity and site of the pain, the skill of the anesthesia provider, and whether any contraindication to regional anesthesia is present. In making the choice, the anesthesiologist should also take into account the equipment, facilities, and the level of monitoring and nursing care available. In general terms, a peripheral nerve block is considered safer than a neuraxial block (2,3).

It is difficult to show clear ‘evidence-based’ benefits of regional anesthesia over other forms of analgesia (3,7). With respect to the pyramid of evidence, apart from many single institution case series, retrospective reviews, and anecdotal reports, there are few prospective randomized controlled studies comparing regional anesthesia with general anesthesia or systemic analgesics in children (6,7). Those that have been performed are often underpowered, have different and varying endpoints, and are usually from single institutions. In addition, more surgery is being performed laparoscopically or thoracoscopically, negating the need for neuraxial blockade where a peripheral nerve block or different analgesic method will suffice (2).

Taking this into consideration, this review, unless stated, confines itself to studies pertaining to children. In some instances, regional anesthesia is combined with adjuvants (opiates, clonidine, ketamine) that may contribute to the risk. The areas covered include the safety of regional blocks in children, analgesia, and consequently other beneficial physiological effects both within and outside the operating room and in the postoperative period.

Safety

Regional anesthesia in children is safe, provided appropriate care and attention to detail are taken. Infants and neonates carry a slightly greater risk of complication, and these age groups should therefore
remain the domain of experienced practitioners (1,4,6–12). Because most regional blocks are performed on anesthetised children, techniques described in adults are not always appropriate for use in children. For example, insufficient negative pressure is generated during inspiration to allow the ‘hanging drop’ technique or other negative pressure detectors to be used safely (13). Intuitively, provided it is used correctly, the advent of ultrasound should reduce complications because most peripheral nerves are relatively superficial in children (14,15). This is supported by a recent meta-analysis of nine studies involving only 649 children from a few centers (16). Large multicentre studies are needed to provide more evidence.

While serious complications have been reported anecdotally (14), the morbidity related to regional anesthesia in children, based on large retrospective (8–10) and prospective studies (1,7,11,12,16–19), is low – approximately 1 : 1000 overall. The majority of complications (e.g., intravascular injection, convulsions, dural puncture) occur at the ‘end of the needle’ when the anesthesiologist is still present and should be successfully managed without long-term sequela. With the advancement of technology and custom designed equipment for children, further improvement in the safety of regional anesthesia can be expected.

Pain relief

Regional anesthesia provides profound analgesia with minimal physiological perturbations or side effects (20–23). Single-shot blocks are limited by the duration of the local anesthetic agent used. However, with the recent development and application of continuous peripheral nerve catheters, more prolonged analgesia is possible (24,25). Regional anesthesia is an effective alternative to systemic analgesics (26,27). This is particularly relevant when systemic opiates are contraindicated in children at risk of opiate-induced respiratory depression (acute) or have become tolerant to their analgesic effects (chronic pain). Regional anesthesia is considered more effective against visceral pain, e.g., bladder spasms following genito-urinary surgery (28,29) than systemic opiates.

The profound analgesia provided by regional anesthesia provides ideal psychological conditions for the recovering child and indeed their family (30,31). Caring for an alert, calm, and cooperative child reduces the workload for nurses in the recovery room because children who are pain free are less inclined to be uncooperative and are less likely to interfere with the operation site, remove dressings, drainage tubes or urinary catheters (32).

An additional benefit of regional anesthesia is that it can be used when general anesthesia is contraindicated, considered technically difficult or associated with increased morbidity and mortality (32). Children or infants in this category include ex-prematures for hernia repair (33–35) or other minor procedures (36,37); those with neuromuscular, (38) metabolic, cardiac, or chronic lung disease; children at risk of malignant hyperthermia or in emergency situations when patients are at risk of aspiration (39). Regional anesthesia can be used to reduce simply fractures in the emergency room (40,41), thereby facilitating earlier discharge and avoiding a long wait for a break in operating room schedule.

A rare but very real benefit of regional anesthesia is that it provides those children with a morbid fear of ‘going to sleep’; those who dislike the ‘loss of control’ during induction; or those who fear ‘never waking up’, an alternative to general anesthesia. In my experience, these children are invariably in their early teens and are well aware of their illness that is usually chronic or life threatening.

Despite the profound analgesia provided by regional anesthesia, consideration should always be given to the psychological aspects of pain. ‘Just because its numb doesn’t mean it doesn’t hurt’ (42) is a quote that drives home this point. Some children particularly those over about 6 years may become very distressed by the absence of sensation over large areas of their body (43). Conversely, in the absence of pain, infants and young children may focus their attention on the ‘pain’ from the intravenous cannula or plaster cast, or be disturbed by awakening in a foreign environment surrounded by strangers. Both situations need to be handled with sensitivity, care, and understanding.

Reduction in general anesthetic requirement (MAC)

Regional anesthesia is generally performed in combination with general anesthesia in children (1,44–47). There are a number of advantages to this practice because anesthetic depth can be reduced by regional anesthesia, thereby potentially reducing the complications of both forms of anesthesia. Immature organ systems (cardiovascular, central nervous and respiratory) are sensitive to the depressant effects of anesthetic drugs. All inhaled anesthetic agents produce dose and agent-related decrease in cardio-respiratory mechanics and central ventilatory control, particularly in neonates, infants, and young children.

The reduction in anesthetic depth (MAC) offers several advantages including (i) avoidance of airway
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Characterized by remarkable hemodynamic stability (21,62–66), and clinically significant decreases in blood pressure are seldom seen in children younger than 8 years of age (66). This obviates the need for volume preload- ing or vasoconstrictors. The reason for this hemody-
namic stability has not been clearly defined but is probably related to the small lower limb capacity in younger children or the ability of those vessels in the unblocked segments to compensate (65).

Regional anesthesia has been used as a sole agent for ex-prematures undergoing inguinal hernia repair to avoid the complications associated with general anesthe-
sia. Inguinal hernia repair under spinal anesthesia (47) or caudal (48,49) is reported to have fewer episodes of apnea, hypoxemia, and bradycardia than those who receive general anesthesia (50,51). The jury is out, though, because recent publications using newer inhalational agents (desflurane, sevoflurane) suggest little dif-
ference (52–54). However, the ex-premature today is very different from those described in the earlier studies. Ventilation strategies have changed, and surfactant is now available resulting in less barotrauma and less severe broncho-pulmonary dysplasia. Comparison with the studies carried out prior to the sevoflurane and desflurane era is therefore questionable.

### Neurotoxicity of general anesthetic agents

The impact that general anesthetic agents have on the developing brain is stimulating great interest and is worth considering. Recent studies in rat and primate models have suggested that anesthetics (NMDA receptor agonists, GABA receptor antagonists) may induce neuronal cell death (apoptosis) in the immature develop-
ing brain (55–60). The neurodegenerative effect seems to be both time- and dose-sensitive (58,60) and is thought to coincide with the peak period for synaptogenesis (60). Intuitively, if exposure to general anesthetic agents can be reduced, then the detrimental effects of inhalational anesthesia could be reduced when used in combination with regional anesthesia.

Furthermore, a recent editorial suggests that local anesthetics may be neuroprotective in adults. Following cardiac surgery, a continuous infusion of lidocaine reduced cognitive dysfunction following cardiopulmo-
ary bypass (61). The study would be difficult to repeat in children but the potential benefits are worthy of further investigation.

### Physiological benefits

#### Hemodynamic stability

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Some argue that the neurodegenerative changes seen in the rat model are secondary to cardiovascular depression leading to low tissue perfusion and hypoxia (60). These insults could also induce neurodegeneration in immature brains. If this were true, it could be argued that regional anesthesia, by maintaining hemody-
namic and respiratory stability in both premature and mature newborns, could reduce the severity of these insults.

### Reduced need for postoperative ventilatory support

Several investigators report that epidural analgesia is more beneficial than conventional opiate therapy in children, particularly infants, undergoing thoracic and upper abdominal procedures (67–71). The reasons sug-
gested include excellent analgesia without the risk of opiate-induced respiratory depression, an improved ventilatory efficiency, (72) improved ventilatory response to hypercapnia (73,74) with bupivacaine (but not lignocaine) (73), and possibly a direct stimulatory effect of bupivacaine on the respiratory center (72,73).

In contrast to intravenous opiates, the need for post-
operative ventilatory support (67,70,71) is reduced by regional anesthesia and, if required, ventilation is of a shorter duration (66), with fewer complications (hyp-
oxemia, pneumonia) (70) and as a consequence shorter intensive care stays (70) This was particularly evident in high-risk children under 2 years of age with neuro-
logical and respiratory disorders undergoing Nissan fundoplication (70).

Neonates and infants in particular are sensitive to the respiratory depressant effects of opiate analgesia. In this age group, epidural analgesia may be indicated when the goal is early extubation [e.g., after tracheoesophageal fistula (6,67) or gastrochisis repair (6,46,75)] or spontaneous ventilation to avoid baro-
trauma (c.g., following congenital diaphragmatic hernia repair). These goals are particularly relevant in developing countries where facilities are limited or stretched (46,67). In addition to analgesia, epidural blockade affords some degree of muscle relaxation (motor blockade). Neonates who have undergone closure of a gastrochisis or omphalocele benefit from both continuous analgesia and abdominal mus-
cle relaxation, whether they are ventilated or not (46,75).

**Analgesia following thoracotomy**

Post thoracotomy pain is considered the most intense pain imaginable (39). Although intravenous opioid infusions are widely used, some authors consider that adequate analgesia cannot be achieved in doses that permit safe spontaneous ventilation (32). Epidural analgesia (67,76,77), paravertebral block (78), intrapleural infusion (79), and intercostal nerve blocks (80,81) have all been shown to be effective for thoracotomy pain. Inadequate analgesia following thoracotomy leads to respiratory dysfunction (39,76,77), while adequate analgesia preserves pulmonary function and may hasten recovery (67,68).

Anecdotal reports of a neonate following tracheoesophageal repair (76) and a toddler following a thoracotomy (76) lend support to the benefits of regional anesthesia. Both children in these reports showed improved respiratory function after restarting epidural analgesia when alternative methods had failed.

Somewhat controversially, proponents of regional anesthesia suggest that spinal or epidural anesthesia is beneficial for both closed- and open-heart surgery (82–84). Neuraxial blocks were placed at least one hour before anticoagulation for cardiopulmonary bypass. Thoracic epidural was considered the most effective (83). The perceived benefits for cardiac surgery include earlier extubation – 89% in the operating theater (83) – and a shorter hospital stay. This may be particularly advantageous following Fontan repair or other single ventricle pathology where spontaneous ventilation is believed to improve pulmonary blood flow and oxygenation (85).

**Hormonal stress response**

Surgical trauma induces a stress response that may have detrimental autonomic, hormonal, metabolic, immunologic/inflammatory, and neurobehavioral consequences. This could seriously effect the outcome of surgery (86), particularly in malnourished or immunocompromised individuals (87). The severity of the stress response varies in direct proportion to the degree of surgical stress (88,89). There is some evidence to suggest that severe stress may be pathological and contributes to postoperative morbidity and mortality; extreme catecholamine responses are associated with the worst outcome (88,89). Numerous publications attest to the efficacy of epidural, spinal, and peripheral nerve blocks in obtunding the neuroendocrine stress response (6,84,87,90–92). The lack of definable endpoints, however, makes it difficult to assess whether one anesthetic technique is superior.

In terms of hormonal levels, studies have shown that stress hormones (epinephrine, norepinephrine, adrenocorticotrophic hormone, cortisol, prolactin) and blood glucose levels are lower following regional anesthesia than after general anesthesia, with (84,90,91) or without (87,92) opiate analgesia, or when the regional block is placed at the end of surgery (92). These lower levels may persist for longer than 24 h after lower abdominal surgery (87). However, in terms of pain scores and other clinical endpoints, no difference could be detected despite these lower hormonal levels. Further studies in larger groups with more appropriate clinical endpoints are required.

**Reduction in intraoperative blood loss**

Clinical experience suggests that general anesthesia supplemented with regional anesthesia produces better operating conditions and a reduction in surgical blood loss in children. Three studies involving infants undergoing cleft lip repair (infraorbital nerve block) (93) or children undergoing tonsillectomy (94) or hypospadias repair (caudal anesthesia) (23) support this hypothesis.

In the hypospadias study, the authors found that the blood loss under general anesthesia alone was almost double that of children who had received a caudal block (31 ± 17 ml vs 16 ± 10 ml) (28). In view of the relatively small volumes involved, it is not surprising that the intraoperative blood loss did not correlate with an increase in heart rate or fall in blood pressure. All children were allowed to breathe spontaneously throughout and mild hypercarbia developed in those who received general anesthesia alone but this was not considered significant enough to have contributed to the increased blood loss. The authors suggest that the reduced blood loss may have contributed to the shorter operating time (92 ± 13 vs 103 ± 14 min) (28).

**Gastrointestinal function**

Earlier return of gut function is a further benefit of regional anesthesia (46,75,95,96). Peristalsis is better maintained with epidural infusions, whereas opiates increase intestinal muscle tone and slow peristalsis (95). The vasodilatory effects of autonomic blockade may improve splanchnic perfusion in necrotizing enterocolitis (46,75,96) and gastroschisis (46,75), whereas opiates increase intestinal muscle tone increasing the risk of anastomotic leaks (96).
Host-defense mechanisms

There is a popularly held belief, particularly among surgeons, that wound infiltration may increase the risk of infection. While the evidence for this is inconclusive, there is increasing evidence both in vitro and in vivo of the beneficial effects of local anesthetics on the inflammatory response (97). Local anesthetics may have an influence on other cellular systems at levels much lower than required for sodium channel blockade. An area of particular clinical interest and relevance is their effect on inflammatory cells [mainly polymorphonuclear leukocytes (PMNL) but also macrophages and monocytes] (97,98).

Overactive inflammatory responses that destroy rather than protect are critical in the development of a number of perioperative disease states. These include postoperative pain syndromes, respiratory distress syndrome, systemic inflammatory response syndrome, and multi-organ failure. Perioperative modulation of these responses is relevant to anesthesiologists and is the subject of an excellent review (97). Local anesthetics may influence inflammatory lung injury, micro-vascular permeability, and ischemia-reperfusion injury in addition to a host of other effects under investigation (97).

In the only comparative study performed in children, halothane was associated with more prolonged depression (>24 h) of PMNL chemiluminescence than after caudal block for lower abdominal surgery (98). Chemiluminescence is used to evaluate oxygen-dependent microbiocidal activity in PMNL. The clinical relevance of this study is unknown but is part of a series of ongoing studies in this field.

Finally, local anesthetics, and not opioids, stimulate the activity of natural killer cells that play an important part in nonspecific cellular-mediated and antitumoral immunity (99,100). To date, there have been no studies in children that show a reduction in neoplastic recurrence following regional blocks.

Outside the operating room

The benefits of regional anesthesia have also been applied outside the operating room.

Caudal blocks have been used to reduce incarcerated inguinal herniae prior to surgery, thereby obviating the need for intravenous sedation in premature infants susceptible to apnoeic spells (101).

Purpura fulminans (102) and tetanus (103) are two particularly painful conditions. The ischemic pain of purpura fulminans or painful tetanic muscle spasms can be effectively managed using continuous epidural infusions or appropriate peripheral nerve blocks (102,103). The autonomic instability associated with such diverse conditions such as tetanus (103) snakebite and pheochromocytoma (104,105) can be successfully managed with epidural blockade.

Other situations where autonomic blockade may be beneficial include vasodilation of ischemic or compromised limbs (106–111) after arterial line (110,111) or umbilical arterial catheter misadventure (112) or penile ischemia (113). Painless placement of percutaneously inserted central catheters (PICC lines) can also be facilitated with an axillary block or femoral nerve block that will both dilate the veins and immobilize the limb (36,37).

Regional anesthesia has a role in unusual causes of intractable pain, postherpetic itch (114), or chronic pain management, particularly those with an autonomic component (115–117). Epidural and peripheral nerve catheters have been used to provide analgesia in terminal patients, thereby moderating opioid requirements and allowing end-of-life care at their preferred location (118).

Economics

In the current climate of cost awareness and economics in medicine, the impact of regional anesthesia will come under close scrutiny. While the anesthetic charges for epidural anesthesia are greater than for intravenous opiates, in terms of overall charges (operating room time, hospital costs, acute pain service), epidural analgesia has been shown to be significantly cheaper in view of the reduced ventilatory support, reduced stay in the ICU, and shorter hospital stays (46,67,70,71,82,83).

With regard to day-stay surgery, earlier discharge is dependant on discharge criteria at a particular institution. While regional anesthesia allows children to be more alert postoperatively and to eat sooner with less nausea and vomiting, controversy exists as to whether these children can be discharged while the residual effects of the block remain. Children have been allowed home earlier with peripheral nerve catheters in situ without significant complications but considerable cost saving (25). The cost savings would therefore be determined by the policy adopted by each institution.

Conclusion

Regional anesthesia is a safe and effective method of analgesia (119), especially as a supplement to general anesthesia. The benefits have been difficult to demonstrate in adults (120), for many of the reasons that
apply to children. In modern anesthesia using an end-point of morbidity and mortality, it is very difficult to show a difference without very large numbers. Clearly defined endpoints need to be drawn to demonstrate a quantifiable improvement in outcome.

The benefits in children as outlined in this manuscript are significant. Enthusiasts would claim that further study is unnecessary and that children deserve the benefit of regional anesthesia in view of the low risks involved. Purists on the other hand would insist on prospective studies to claim any benefit. Some less experienced anesthesiologists are reluctant to offer the benefit of some of the more difficult blocks because they consider the risk too great, particularly in the face of adverse medico-legal climate and lack of evidence. Purists who have practiced regional anesthesia in view of the low risks involved. Purists on the other hand would insist on prospective studies to claim any benefit. Some less experienced anesthesiologists are reluctant to offer the benefit of some of the more difficult blocks because they consider the risk too great, particularly in the face of adverse medico-legal climate and lack of evidence.

Most of the popular regional anesthetic techniques are easy to perform, but simply because a block can be performed does not mean that it is necessarily the best choice for a particular patient. Each block requires careful consideration. With the advent of ultrasound-guided nerve blocks, together with ongoing improvement in equipment for use in children, meticulous attention to detail, careful monitoring, and regular audit, the safety of regional anesthesia in infants and children will continue to improve and more children should benefit.

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Conflict of interest
No conflicts of interest declared.

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