Bladder exstrophy in a neonate at risk of transient myasthenia gravis: a role for remifentanil and epidural analgesia

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Infants born to mothers with myasthenia gravis may exhibit a transient form of the disease, with similar sensitivity to non-depolarizing neuromuscular blocking drugs. We report the case of an infant at risk who required major surgery when 48 h old for closure of bladder exstrophy. A combined epidural–general anaesthetic technique, with remifentanil supplementation, enabled us to avoid unnecessary neuromuscular blocking drugs and prolonged intensive care, which had been anticipated. The potential benefits of remifentanil and epidural analgesia in neonates are discussed.

Keywords: anaesthesia, paediatric; neonate; analgesic techniques, epidural; analgesics opioid, remifentanil; complications, myasthenia gravis; complications, bladder exstrophy

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Between 10 and 15% of infants born to mothers with myasthenia gravis may demonstrate a transient form of the disease. Symptoms are unrelated to the severity of the maternal disease and depend on the proportion of IgG transmitted across the placenta. An affected infant displays muscle weakness and an increased sensitivity to non-depolarizing neuromuscular blocking drugs.1 These symptoms improve with maturation of the infant’s immune system, a feature which distinguishes transient neonatal myasthenia from other forms of congenital myasthenia gravis.2

We report the anaesthetic management of an at risk neonate who presented for urgent repair of bladder exstrophy in the first 2 days of life. This is a major procedure involving both abdominal and pelvic surgery, and postoperative leg traction. Potential transient neonatal myasthenia could complicate the clinical management because of the unpredictable response to neuromuscular blocking drugs. Epidural analgesia may be used to supplement general anaesthesia for surgery in such neonates, providing postoperative analgesia and avoiding the respiratory depressant effect of opioid analgesics.3 In practice, it is difficult to assess the effectiveness of epidural block in a neonate until recovery from general anaesthesia is complete, and opioids are usually required for intraoperative analgesia. The pharmacological properties of remifentanil suggest it should be a useful analgesic supplement to combined epidural–general anaesthesia for major surgery in neonates.

Case report
A 2-day-old baby boy, born at 37 weeks’ gestation, weighing 2.7 kg, presented for urgent closure of bladder exstrophy. Apart from an associated epispadias, there were no other congenital abnormalities. His mother, however, had a mild form of myasthenia gravis which had been diagnosed a few years earlier when she failed to recover normally from a general anaesthetic. The need for urgent surgery precluded formal investigation of possible transient myasthenia, although the baby appeared to have normal muscle tone. Assessment of bulbar symptoms was also incomplete as the baby had not yet been fed: feeding distress is an important feature of the disorder.

Preoperative serum electrolyte and urea concentrations were normal and haemoglobin concentration was 19 g dl⁻¹. No premedication was prescribed and anaesthesia was induced in the operating theatre when baseline pulse oximetry, ECG and non-invasive arterial pressure monitoring were established. Anaesthesia was induced with thiopental 20 mg i.v. An initial dose of atracurium 1.5 mg facilitated tracheal intubation (using a 3.5-mm tracheal tube) and positive pressure ventilation (Siemens Servo D) with capnographic monitoring. An indwelling arterial catheter was inserted for direct pressure measurement and intermittent blood-gas analysis. Anaesthesia was induced with thiopental 20 mg i.v. An initial dose of atracurium 1.5 mg facilitated tracheal intubation (using a 3.5-mm tracheal tube) and positive pressure ventilation (Siemens Servo D) with capnographic monitoring. An indwelling arterial catheter was inserted for direct pressure measurement and intermittent blood-gas analysis. Anaesthesia was maintained with 60% nitrous oxide in oxygen, supplemented with isoflurane. Remifentanil was infused via a dedicated cannula at an initial dose of 0.25 µg kg⁻¹ min⁻¹ for 20 min.

An epidural catheter (0.63 mm in diameter, Portex) was introduced via the sacral hiatus using a 19-gauge Tuohy needle and advanced so that the tip was situated between the seventh and eighth thoracic vertebrae. A bolus dose of 0.2% ropivacaine 1.4 ml was given and an infusion started at 0.5 ml h⁻¹. Using clinical signs of depth of anaesthesia,
it was possible to reduce the concentrations of isoflurane and remifentanil as surgery progressed, from 1% to 0.5% and from 0.25 to 0.025 µg kg⁻¹ min⁻¹, respectively. Maintenance fluid of 4% dextrose in 0.18% saline was infused at 12 ml h⁻¹. Blood loss was assessed using swab losses and serial packed cell volume measurements and replaced with human albumin solution (4.5%) and packed red cells, titrated to the haemodynamic response.

Surgery, which lasted 4 h, involved mobilization of the bladder and its relocation on the pelvis. Bilateral iliac osteotomies were necessary to restore normal anatomy of the pelvic ring. At the end of the procedure, the legs were placed in traction, flexed to 90° at the hips and the knees. Isoflurane was stopped at completion of skin closure and remifentanil infusion discontinued after dressings and traction had been applied. Within 10 min the baby was awake, breathing comfortably, warm and clinically well perfused. We did not monitor neuromuscular block other than by clinical observation because, in our experience, neuromuscular monitoring in neonates is practically and technically difficult. No antagonism of neuromuscular blocking drugs was necessary and the baby’s trachea was extubated 10 min later in the operating theatre before being transferred to the intensive care unit for further observation. He was discharged to the ward after 7 h, as it was thought that a lower level of nursing dependency was now appropriate. The epidural infusion of ropivacaine was continued at a rate of 0.5 ml h⁻¹ for 4 days after operation, without complications. During this time, four doses of paracetamol and two of codeine were needed orally for supplementary analgesia.

Discussion

Transient neonatal myasthenia gravis should not be confused with congenital myasthenia gravis. The former occurs in 10–15% of infants born to mothers with the disease and is a result of placental transfer of antibodies to acetylcholine receptors. Symptoms, the severity of which are unrelated to those of the mother, appear within 72 h of birth and persist for several days. It is rare for symptoms to persist after 3 months. The commonest presentation is that of a floppy baby with a weak cry, shallow respiration and feeding distress who, rarely, requires respiratory support. The diagnosis is confirmed by the edrophonium test, and treatment, where necessary, is with oral pyridostigmine. The condition resolves completely as the infant’s immune system matures and there are no long-term effects. Congenital myasthenia gravis, however, is more serious and is caused by an inherited abnormality of the acetylcholine receptor. Weakness and hypotonia are more severe and respiratory support is often required.

It was coincidental that this baby had a major genitourinary abnormality. In classical extrophy, absence of the anterior wall of the bladder and the overlying abdominal wall result in exposure of the bladder cavity to the atmosphere. It is associated with epispadias and separation of the symphysis pubis. Surgical treatment is staged, the first operation involving closure of the bladder and abdominal walls, and relocation of the bladder in the pelvis. Subsequent operations are needed to repair the epispadias and achieve urinary continence.

Our choice of anaesthetic technique took account of the desirability of avoiding unnecessary non-depolarizing neuromuscular blocking drugs and their reversal agents in addition to the need for potent analgesia. While i.v. morphine would certainly have provided good intraoperative and postoperative analgesia, this was unlikely to be achieved without the need for postoperative respiratory support, given the extent of the surgical procedure. The clinical picture was likely to be complicated further by residual neuromuscular block. In our experience, there are considerable practical difficulties in monitoring neuromuscular block during neonatal anaesthesia other than by clinical observation. Therefore, we aimed to limit administration of atracurium to that necessary for airway control and ventilation and to use the neuromuscular blocking properties of epidural analgesia, supplemented by the newer opioid analgesic, remifentanil.

Combined epidural–general anaesthetic techniques are increasingly popular for major surgery in neonates. The usual advantage is that i.v. opioids can be avoided, or reduced, decreasing the risks of postoperative respiratory depression yet still providing good postoperative analgesia. Attenuation of the stress responses to surgery has also been demonstrated, although this has not yet been linked directly to improvements in outcome for infants undergoing non-cardiac surgery. Neonates, unlike older infants, do not seem distressed by epidural motor or sensory block and additional sedation is usually unnecessary. There have been few formal comparative studies of epidural drug regimens in neonates, the commonest practices being to infuse bupivacaine or lidocaine. Adding an opioid to the epidural infusion increases the risk of respiratory depression in neonates and usually precludes management outside the intensive care unit. Clinical management is confounded further if the epidural does not relieve pain satisfactorily and conversion to systemic opioids is necessary. In adults, the clinical profile of ropivacaine is similar to that of bupivacaine, albeit with less motor block. Our experience of ropivacaine in older children suggests it is an acceptable alternative. Furthermore, animal studies in which various local anaesthetic drugs were infused i.v., suggest that signs of toxicity appear at a greater plasma concentration of ropivacaine compared with bupivacaine. Ropivacaine may offer an increased margin of safety in neonates, in whom the toxicity of local anaesthetics is poorly understood.

The introduction of remifentanil is stimulating a re-evaluation of the use of potent opioids as part of balanced anaesthetic techniques, although data in children are few. Rapid metabolism by non-specific plasma esterases gives a short elimination half-life of 5–8 min which is unaffected by hepatic and renal function. Accumulation is therefore unlikely, even after prolonged infusion. This may be
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particularly desirable in neonatal anaesthesia when an alternative means of postoperative analgesia can be provided, such as epidural block. To our knowledge, there have been no other reports of the use of remifentanil in a neonate, although our experience of this drug in older children is that dosing regimens are similar to those described for adults, on a weight-related basis. In neonates, however, we have found opioid side effects of hypotension and bradycardia to be more common, particularly on bolus administration of the drug. Our practice when infusing remifentanil as part of a balanced anaesthetic technique with nitrous oxide and isoflurane is to prepare a dilution of 0.75 mg in 50 ml of 5% dextrose, such that an infusion rate of 1 ml h\(^{-1}\) delivers 0.25 µg kg\(^{-1}\) min\(^{-1}\). The infusion rate is then adjusted in anticipation of noxious stimuli, titrating to the haemodynamic response. We find that less isoflurane is required and that recovery times appear faster than when conventional inhalation anaesthesia is used. Further studies of doses in neonates are in progress.

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