

CLINICAL PRACTICE

Newborns should be receiving premedication before elective intubation

M S Raban, Y Joolay, A R Horn, M C Harrison

Dr Shukri Raban completed his neonatal fellowship at Groote Schuur Hospital, Cape Town, South Africa, and qualified as a neonatologist in 2012. His main interest is improving infant nutrition, and he is currently involved in research to improve breastmilk provision in the neonatal unit. Additional interests include clinical governance, infection surveillance and less invasive measures to provide surfactant to infants. Dr Yaseen Joolay is a neonatologist at Groote Schuur Hospital. An avid fan of innovative technologies, his current interests are quality improvement, standardisation of practices and the appropriate application of technologies in neonatal care. Assoc. Prof. Alan Horn is a neonatologist at Groote Schuur Hospital. He was recently awarded a PhD for his research on hypoxic ischaemic encephalopathy – he has a special interest in the use of amplified electroencephalography and therapeutic cooling and has published work in this field. Assoc. Prof. Michael Harrison is a neonatologist and head of the Division of Neonatal Medicine, Groote Schuur Hospital and Department of Paediatrics, Faculty of Health Sciences, University of Cape Town, to which all the authors are affiliated. He completed his paediatric and subspecialty training in the UK. He is an advocate for clinical governance and places strong emphasis on translational research.

Corresponding author: M S Raban (shukriraban@yahoo.co.uk)

Background. Intubation is a common neonatal procedure. Premedication is accepted as a standard of care, but its use is not universal and wide variations exist in practice.

Objective. To evaluate current practices for premedication use prior to elective neonatal intubation in South Africa (SA).

Method. We invited 481 clinicians to participate in a cross-sectional web-based survey.

Results. We received responses from 28.3% of the clinicians surveyed; 54.1% were from the private sector and 45.9% from the state sector. Most respondents worked in medium-sized neonatal units with six to ten beds. Most paediatricians (76.0%) worked in the private sector, and 78.6% of neonatologists in the state sector. Premedication was practised by 71.9% of the respondents, but only 38.5% of neonatal units had a written policy. Sedatives were used for premedication by 63.2% of the respondents. Midazolam (41.5%), morphine (34.0%) and ketamine (20.8%) were most commonly used. Muscle relaxants and atropine were not routinely administered. Suxamethonium was the muscle relaxant of choice. Varied combinations of agents or single agents were used. Midazolam used alone was the preferred option.

Conclusion. This first survey of premedication for neonatal intubation in SA revealed variations in practice, with a minority of clinicians following a written policy. The findings can be used to benchmark practice and inform the design of local collaborative trials aimed at determining optimal premedication prior to neonatal intubation. The survey demonstrates clinicians' reluctance to participate in surveys, suggesting a need for a national collaborative network to obtain representative data.

S Afr Med J 2014;104(12):846-849. DOI:10.7196/SAMJ.8305



Endotracheal intubation is a common neonatal procedure and essential for the provision of neonatal intensive care. The procedure induces noxious stimuli often associated with adverse physiological events such as raised intracranial pressure,^[1] hypoxaemia and cardiovascular instability.^[2] Premedication regimens may include a vagolytic to reduce vagal-induced bradycardia, a narcotic/sedative agent that attenuates increases in systemic blood pressure, and a muscle relaxant that attenuates increases in intracranial pressure.^[3]

Recent studies have shown that premedication for elective and semi-urgent intubation of infants significantly improves intubation conditions, decreases the time and number of attempts needed to complete the intubation procedure, and minimises the potential for intubation-related airway trauma.^[4-6] However, despite the growing body of evidence and acceptance of premedication as a standard of care, its use is still not universal, and wide variations occur in practice.^[7,8]

Premedication practices have been surveyed in Europe,^[7,9,10] North America^[8,11] and Australia.^[12] The European surveys had a profound effect on current practice. Whyte *et al.*^[7] demonstrated in a study conducted in 1998 that 63% of UK neonatal units did not use

premedication prior to intubation, their study prompting much discussion. A decade later, when the survey was repeated, ≥90% of neonatal units had adopted premedication as standard of care.^[9,10]

Because current neonatal premedication practices have not previously been surveyed in South Africa (SA), we designed a survey with the objective of determining the current practice and standard of care. This survey may provide data that could inform the design of collaborative trials and/or stimulate debate that ultimately leads to change and standardisation of practice.

Methods

The study was designed as a cross-sectional survey of clinicians working in SA state and private neonatal intensive care units. This research was approved by the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town.

Potential participants were identified from an online listing of 147 neonatal intensive care units in hospitals across SA on the Medpages directory website.^[13] The names and contact details of the clinicians working in those units were obtained by searching the websites of the respective hospitals. Additional names and contact details of clinicians involved in neonatal care

were obtained from a local departmental database. Clinicians who did not treat neonates in their practice were excluded. Clinicians did not receive incentives to participate in the survey.

The survey questionnaire was created and hosted using Survey Monkey, an online survey website. The questionnaire enabled compilation of data regarding use of premedication and whether a written policy existed for sedating preterm infants before elective or semi-elective intubation. The questionnaire was designed to determine which agent/s were most used for premedication, as well as the doses used. The questionnaire was brief, taking no more than 3 minutes to complete. Each question addressed a single point and in most cases required a 'yes' or 'no' response. An e-mail containing an individualised link to the survey was sent to 481 clinicians on 1 October 2013. The Survey Monkey collector tool collected all responses anonymously and automatically sent reminder e-mails to those who had not responded. Survey collection closed on 14 November 2013.

Data analysis

Responses were exported to a Microsoft Excel file. Data were analysed with Stata version 12 (Stata Corporation, USA). Chi-square and Fisher's exact tests were used for comparison of categorical variables. Descriptive results were expressed as numbers and proportions (%). A *p*-value of <0.05 was considered significant.

Table 1. Characteristics of neonatal units surveyed (N=136)

	<i>n</i> (%)
Nature of practice	
Private health sector	66 (54.1)
Public health sector	56 (45.9)
Rank	
Medical officer	9 (6.6)
Registrar	6 (4.4)
Paediatrician	78 (57.4)
Neonatologist	28 (20.6)
Other specialist	5 (3.7)
Not a medical doctor	10 (7.4)
ICU beds	
0	3 (2.5)
1 - 5	35 (28.7)
6 - 10	50 (41.0)
>10	34 (27.9)

Results

We received responses to 136 of the 481 emails sent (28.3%). The characteristics of the respondents surveyed are shown in Table 1. Sixty-six responses (54.1%) were from clinicians in the private sector and 56 (45.9%) from those in the state sector. The majority of respondents were paediatricians or neonatologists. The majority of paediatricians (76.0%) worked in the private sector, whereas 78.6% of neonatologists worked in the state sector, typically in medium-sized neonatal units with six to ten beds.

A subgroup analysis comparing premedication practices between the public and private sectors is reported in Table 2. A written policy was used by a minority of clinicians, more often in the public sector (*p*<0.0001).

Premedication prior to intubation was practised by 71.9% of respondents; however, only 38.5% of neonatal units had a written policy. The respondents routinely used sedatives for premedication, but not

muscle relaxants or atropine. These data are reported in Table 3 and Fig. 1. Midazolam, morphine and ketamine were the most commonly used sedative agents (Fig. 2). When muscle relaxants were administered, suxamethonium (95.2%) was the muscle relaxant of choice.

Table 4 illustrates varied combinations of agents or single agents used for premedication. Seven premedication drugs were used in 16 different combinations/regimens, utilising one to three drugs. Midazolam was the drug most commonly used as a single agent.

Table 5 illustrates the drug dose ranges. Most respondents stated specific doses for the choice of drug used: 33.3% specified a morphine dose of 0.1 mg/kg, whereas 39.0% said that they would administer a dose of 0.2 mg/kg. Midazolam dosing varied, respondents using doses of 0.1 mg/kg (36.4%), 0.15 mg/kg (13.6%), 0.2 mg/kg (22.7%) and 0.4 mg/kg (4.5%). For suxamethonium, 55.0% of respondents used a dose of 2 mg/kg.

Table 2. Subgroup analysis

Premedication practice	Private sector, <i>n</i> (%)	Public sector, <i>n</i> (%)	<i>p</i> -value
Written policy present	15 (31.9)	32 (68.0)	<0.0001
Routine use of any premedication agent	46 (52.9)	41 (47.1)	0.8
Routine use of sedatives	25 (45.5)	30 (54.6)	0.13
Routine use of muscle relaxants	10 (47.6)	11 (52.4)	0.62
Routine use of atropine	15 (45.5)	18 (54.6)	0.315

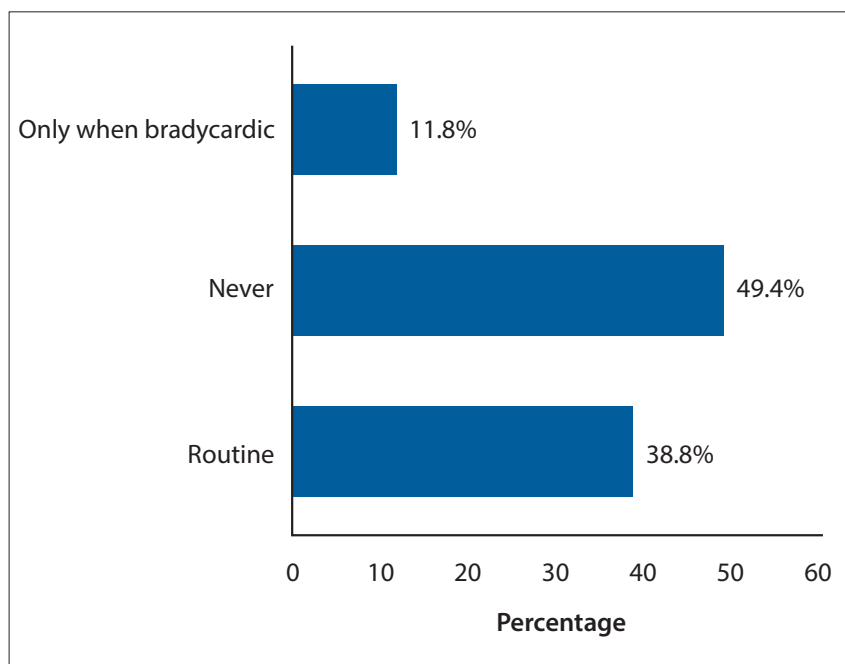


Fig. 1. Atropine use for premedication.

Table 3. Premedication practices

Premedication practice	Yes, n (%)	No, n (%)
Written policy	47 (38.5)	75 (61.5)
Use of premedication	87 (71.9)	34 (28.1)
Routine use of sedatives	55 (63.2)	32 (36.8)
Routine use of muscle relaxants	21 (24.4)	65 (75.6)

Table 4. Combinations of premedication used

Agents	Respondents (N=87) n (%)
Midazolam + suxamethonium + atropine	1 (1.15)
Midazolam + atropine (when bradycardic)	5 (5.7)
Midazolam alone	16 (18.4)
Morphine + suxamethonium + atropine	7 (8.0)
Morphine + atropine	2 (2.3)
Morphine alone	7 (8.0)
Morphine + atropine (when bradycardic)	2 (2.3)
Ketamine + suxamethonium + atropine	6 (6.9)
Ketamine + cisatracurium + atropine	1 (1.15)
Ketamine + atropine	4 (4.6)
Fentanyl + suxamethonium + atropine	1 (1.15)
Propofol alone	1 (1.15)
Suxamethonium alone	1 (1.15)
Suxamethonium + atropine	4 (4.6)
Atropine alone	7 (8.0)
Atropine when bradycardic	3 (3.4)
Answered 'yes' for premed, no agents ticked	19 (21.8)

Table 5. Doses for premedication drugs

Drug	Dose
Fentanyl	10 µg/kg
Ketamine	1 - 2 mg/kg
Midazolam	0.05 - 0.4 mg/kg
Morphine	0.05 - 0.2 mg/kg
Propofol	1 - 2 mg/kg
Suxamethonium	1 - 2 mg/kg

Discussion

A greater understanding of neonatal pain and the knowledge that noxious stimuli such as intubation may have long-term deleterious effects^[13] have prompted consensus statements^[14-16] advocating the use of premedication as standard of care.

This study illustrates that almost 30% of the SA clinicians surveyed were not administering premedication to infants before elective or semi-elective intubation,

in stark contrast to practice in the UK or Australasia, where recent surveys^[9,10,12] indicate that >90% of units are providing premedication. No consensus exists regarding the choice of agent/s, their dose/s or the ideal route of administration,^[6] mirroring the findings of the present study and other surveys.^[7-12]

Suxamethonium, as in other national surveys,^[7-12] was the most commonly used muscle relaxant and is currently considered to be the best choice^[17] because of its rapid onset, short duration of action and good side-effect profile.

In contrast to findings in the other national surveys,^[7-12] midazolam was the preferred sedative in this SA study. Many participants used midazolam as the only premedication drug. Midazolam, a short-acting benzodiazepine with sedative properties, is inappropriate^[17] because it has no analgesic properties. There are additional pitfalls to the use of midazolam as a single agent for intubation: Harte *et al.*,^[18] examining the

haemodynamic effect and pharmacokinetic properties of midazolam, demonstrated no mitigation of the physiological changes attributed to intubation and found that the drug was associated with serious adverse effects during intubation. The use of midazolam has also been associated with hypotension and adverse neurological outcomes.^[19,20] A Cochrane review found no evidence to support the use of midazolam as a sedative for infants, particularly preterm ones.^[21] Infants receiving midazolam had longer hospital stays, and there were more adverse effects in the midazolam group when compared with placebo.^[21]

A survey of premedication practices in the UK by Singh *et al.*^[22] found the combination of fentanyl, atropine and suxamethonium to be the most common, followed by morphine, atropine and suxamethonium. A recent randomised controlled trial (RCT) in which either morphine alone or placebo was given 5 minutes before intubation demonstrated inability of morphine to reduce either the adverse physiological changes attributed to intubation or the time required to complete the intubation process.^[23] Moreover, safety concerns regarding the use of morphine for premedication in preterm infants have been raised, as it has been associated with prolonged amplified electroencephalography (aEEG) depression, independent of blood pressure changes.^[24] Fentanyl is preferred to morphine, as its more rapid onset of action may improve pain control during intubation.^[25] Hamon *et al.*^[26] have shown that short-term fentanyl infusion in preterm infants is not associated with changes in systemic and cerebral perfusion pressures.

Propofol was listed by one respondent as their premedication drug of choice. Propofol is a hypnotic agent without anaesthetic properties. Spontaneous breathing effort is maintained during the intubation process. Ghanta *et al.*^[5] compared propofol with a combination of morphine, atropine and suxamethonium, which took 5 times longer to prepare. They reported faster intubation times, better oxygen saturation maintenance and shorter recovery times in the propofol group, and there was no difference in bradycardia or hypotension between the two groups.^[5] A paucity of data remains regarding the use of propofol in infants; the Cochrane review by Shah *et al.*^[27] only included the 63 infants in Ghanta *et al.*'s RCT. There are also significant concerns regarding the safety of propofol, Welzing *et al.*^[28] demonstrating a significant drop in arterial blood pressure when propofol was injected as a fast push. Current pharmacokinetic

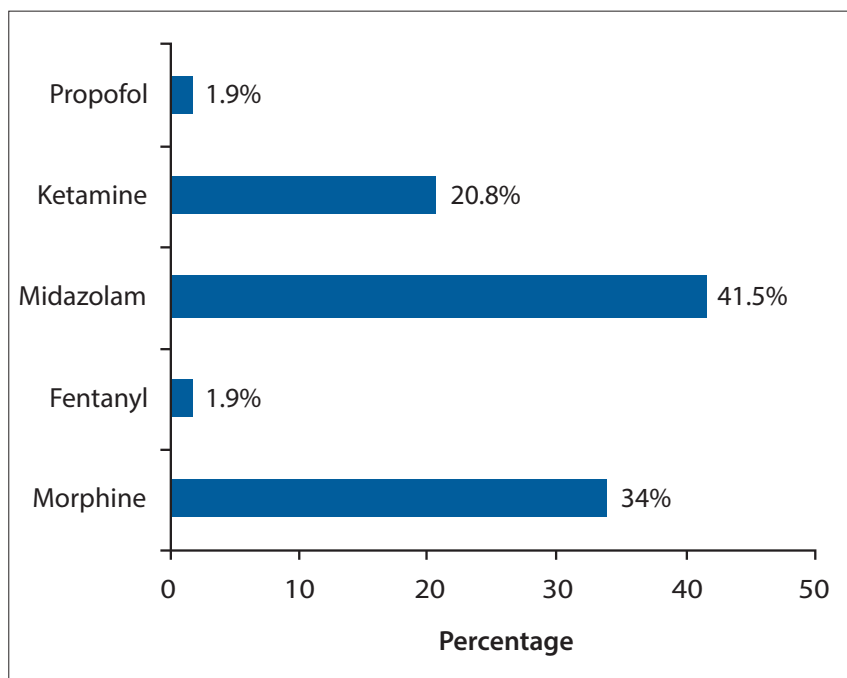


Fig. 2. Sedative agents used.

studies on the use of propofol in infants indicate marked inter-individual variability and reduced clearance of propofol.^[29] The Exploratory Propofol Dose Finding Study in Neonates (NEOPROP) is currently under way and aims to evaluate pharmacokinetics and pharmacodynamics of propofol and to determine the optimal dose in infants.^[30] Following identification of a safe dose, RCTs are needed to assess safety and efficacy of propofol, both as a single agent and in combination with an analgesic agent.

The UK and Australasian surveys enjoyed high response rates from clinicians surveyed. The low rate of response to the current survey may not reflect true premedication practices, as SA doctors respond poorly to mail surveys despite high internet penetration, which influenced our decision to conduct a web-based survey.^[31]

This is the first study to survey premedication practice prior to elective neonatal intubation in SA. The findings highlight a wide variation in practices and the need for written policies, particularly in the private sector. Further research is needed to determine the outcomes associated with premedication, the most appropriate agent/s and their optimal dose/s. A national network of neonatal units needs to be established to ensure representative data collection. The findings of this study could be used to inform local collaborative trials aimed

at studying premedication for intubation in the neonatal period. Importantly, this survey may stimulate debate and discussion, culminating in a national premedication practice guideline.

Acknowledgements. The authors thank all the participants for providing data for this survey.

- Friesen RH, Honda AT, Thieme RE. Changes in anterior fontanel pressure in preterm neonates during tracheal intubation. *Anesth Analg* 1987;66(9):874-878. [http://dx.doi.org/10.1213/00000539-198709000-00012]
- Kelly MA, Finer NN. Nasotracheal intubation in the neonate: Physiologic responses and effects of atropine and pancuronium. *J Pediatr* 1984;105(2):303-309. [http://dx.doi.org/10.1016/S0022-3476(84)80137-7]
- Mayock DE, Gleason CA. Pain and sedation in the NICU. *Neoreviews* 2013;14(1):e22-e31. [http://dx.doi.org/10.1542/neo.14-1-e22]
- Pereira e Silva Y, Gomez RS, Marcato J, Maximo TA, Barbosa RE, Simões e Silva AC. Morphine versus remifentanyl for intubating preterm neonates. *Arch Dis Child Fetal Neonatal Ed* 2007;92(4):F293-F294. [http://dx.doi.org/10.1136/adc.2006.105262]
- Ghanta S, Abdel-Latif ME, Lui K, Ravindranathan H, Awad J, Oei J. Propofol compared with the morphine, atropine, and suxamethonium regimen as induction agents for neonatal endotracheal intubation: A randomized controlled trial. *Pediatrics* 2007;119(6):e1248-e1255. [http://dx.doi.org/10.1542/peds.2006-2708]
- Carbajal R, Eble B, Anand KJS. Premedication for tracheal intubation in neonates: Confusion or controversy? *Semin Perinatol* 2007;31(5):309-317. [http://dx.doi.org/10.1053/j.semper.2007.07.006]
- Whyte S, Birrell G, Wyllie J, Woolf A. Premedication before intubation in UK neonatal units. *Arch Dis Child Fetal Neonatal Ed* 2000;82(1):F38-F41. [http://dx.doi.org/10.1136/fn.82.1.F38]
- Sarkar S, Schumaker RE, Baumgart S, Donn SM. Are newborns receiving premedication before elective intubation? *J Perinatol* 2006;26(5):286-289. [http://dx.doi.org/10.1038/sj.jp.7211499]
- Kelleher J, Mallya P, Wyllie J. Premedication before intubation in UK neonatal units: A decade of change? *Arch Dis Child Fetal Neonatal Ed* 2009;9(4):F332-F335. [http://dx.doi.org/10.1136/adc.2008.154518]
- Chaudhary R, Chonat S, Gowda H, Clarke P, Curley A. Use of premedication for intubation in tertiary neonatal units in the

- United Kingdom. *Paediatr Anaesth* 2009;19(7):653-658. [http://dx.doi.org/10.1111/j.1460-9592.2008.02829.x]
- Ziegler JW, Todres ID. Intubation of newborns (Letter). *Am J Dis Child* 1992;146(2):147-149.
- Wheeler B, Broadbent R, Reith D. Premedication for neonatal intubation in Australia and New Zealand: A survey of current practice. *J Paediatr Child Health* 2012;48(11):997-1000. [http://dx.doi.org/10.1111/j.1440-1754.2012.02589.x]
- Medpages. South Africa - Hospital Depts - Neonatal ICU - Total records per region. <http://medpages.co.za> (accessed 15 August 2011).
- American Academy of Pediatrics, Committee on Fetus and Newborn; American Academy of Pediatrics, Section on Surgery; Canadian Paediatric Society, Fetus and Newborn Committee. Prevention and management of pain in the neonate: An update [published correction appears in *Pediatrics* 2007;119(2):425]. *Pediatrics* 2006;118(5):2231-2241. [http://dx.doi.org/10.1542/peds.2006-2277]
- Kumar P, Denson SE, Mancuso TJ, and Committee on Fetus and Newborn, Section on Anesthesiology and Pain Medicine. Premedication for nonemergency endotracheal intubation in the neonate. *Pediatrics* 2010;125(3):608-615. [http://dx.doi.org/10.1542/peds.2009-2863]
- Anand KJS; International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001;155(2):173-180. [http://dx.doi.org/10.1001/archpedi.155.2.173]
- Barrington KJ; Canadian Paediatric Society Fetus and Newborn Committee. Premedication for endotracheal intubation in the newborn infant. *Paediatr Child Health* 2011;16(3):159-164.
- Harte GJ, Gray PH, Lee TC, Steer PA, Charles BG. Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates. *J Paediatr Child Health* 1997;33(4):335-338. [http://dx.doi.org/10.1111/j.1440-1754.1997.tb01611.x]
- Jacqz-Aigrain E, Daoud P, Burtin P, et al. Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. *Lancet* 1994;344(8923):646-650. [http://dx.doi.org/10.1016/S0140-6736(94)92085-0]
- Anand KJS, McIntosh N, Lagercrantz H, et al. Analgesia and sedation in preterm neonates who require ventilatory support: Results from the NOPAIN trial. *Arch Pediatr Adolesc Med* 1999;153(4):331-338. [http://dx.doi.org/10.1001/archpedi.153.4.331]
- Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database of Systematic Reviews* 2012, Issue 6. Art. No.: CD002052. [http://dx.doi.org/10.1002/14651858.CD002052.pub2]
- Singh Y, Lester M, Ng V, Miall L. Premedication for neonatal intubation: Current practice in the tertiary neonatal units in the United Kingdom. *Arch Dis Child* 2012;97(Suppl 2):A1-A539. [http://dx.doi.org/10.1136/archdischild-2012-302724.1636]
- Lemyre B, Doucette J, Kalyn A, Gray S, Marrin M. Morphine for elective endotracheal intubation in neonates: A randomized trial. *BMC Pediatr* 2004;4:20. [http://dx.doi.org/10.1186/1471-2431-4-20]
- Norman E, Wikström S, Rosén I, Fellman V, Hellström-Westas L. Premedication for intubation with morphine causes prolonged depression of electrocortical background activity in preterm infants. *Pediatr Res* 2013;73(1):87-94. [http://dx.doi.org/10.1038/pr.2012.153]
- Brunson LL, Lazo JS, Parker KL, eds. Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. 11th ed. New York: McGraw Hill, 2006.
- Hamon I, Hascoet JM, Debiche A, Vert P. Effects of fentanyl administration on general and cerebral haemodynamics in sick newborn infants. *Acta Paediatr* 1996;85(3):361-365. [http://dx.doi.org/10.1111/j.1651-2227.1996.tb14033.x]
- Shah PS, Shah VS. Propofol for procedural sedation/anaesthesia in neonates. *Cochrane Database of Systematic Reviews* 2011, Issue 3. Art. No.: CD007248. [http://dx.doi.org/10.1002/14651858.CD007248.pub2]
- Welzing L, Kribs A, Eifinger F, Huenseler C, Oberthuer A, Roth B. Propofol as an induction agent for endotracheal intubation can cause significant arterial hypotension in preterm neonates. *Pediatric Anesthesia* 2010;20(7):605-611. [http://dx.doi.org/10.1111/j.1460-9592.2010.03330.x]
- Allegaert K. Is propofol the perfect hypnotic agent for procedural sedation in neonates? *Curr Clin Pharmacol* 2009;4(2):84-86. [http://dx.doi.org/10.2174/157488409788184927]
- Thewissen L. Exploratory Propofol Dose Finding Study in Neonates (NEOPROP). *ClinicalTrials.gov* identifier: NCT01621373 [http://clinicaltrials.gov/show/NCT01621373].
- Joolay Y, Horn AR, Harrison MC. Therapeutic hypothermia and hypoxic ischaemic encephalopathy: Opinion and practice of paediatricians in South Africa. *J Perinatol Med* 2012;40(4):447-453. [http://dx.doi.org/10.1515/jpm-2011-0292]

Accepted 14 August 2014.