National Essential Medicine List Medication for Adult Hospital Level Review Process Component: Anaesthesia

Date: 2 September 2015

Medication: Sodium citrate solution

Indication: To reduce the risk of aspiration pneumonitis in patients undergoing Caeserean section.

Review question: Amongst pregnant women undergoing surgery (elective or unplanned) is sodium citrate solution more efficacious than current standard of care, available on the National Essential Medicines List (proton pump inhibitors)?

Introduction: This review followed on after the submission of a motivation from the Western Cape for the "inclusion of sodium citrate preparation on the National Essential Medicines list, for use for pre-medication for anaesthesia at caesarean Section, at all levels of care".

Acid suppression forms part of routine practice in patients who undergo caesarean section as prophylaxis against aspiration pneumonitis. The risk of harm increases when the gastric aspirate aspirated into the lungs is greater than 25 mL and the pH is less than 2.5[i].

NICE[ii], European Society of Anaesthesiology[iii] and American Society of Anesthesiologists[iv] recommends antacid prophylaxis in obstetric women undergoing surgical procedures, either planned or unplanned. A UK survey showed that there was a 3-11% greater risk of failed intubation in pregnant women as opposed to non-pregnant women[v]. Risk factors included obesity, structural oropharyngeal obstructions (missing maxillary incisors, protruding maxillary incisors, single maxillary incisor and receding mandible). It was reported that "difficult tracheal intubation, often unexpected, had been identified as the commonest contributory factor to anesthetic-related maternal death". A US observational study[vi] showed that amongst women with the greatest preoperative risk (American Society of Anesthesiologists score > or = 4) that received a general anesthetic, one maternal death occurred due to a failed intubation. The authors of this study stated that generally, regional anaesthesia appears to be the preferred approach for cesarean delivery.

Available local epidemiology data reported that 7% of maternal deaths associated with general anaesthesia were due to gastric aspiration for the period 1999 to 2001; and 5% for the priod 2002 to 2004[vii].. Furthermore, the Saving Mother's report (6th edition:2011-2013) reported that a "lack of appropriately trained doctors was recorded as a significant factor in 47%, 27% 24% and 19% of maternal deaths due to anaesthesia, obstetric haemorrhage, pregnancy related sepsis and complications of hypertension"[viii].

Search strategy: A medline search was performed using the following search strategies:
Database(s): Ovid MEDLINE(R) 1946 to August Week 3 2015

Search Strategy: Antacids

	Searches	Results
1	exp *Pneumonia, Aspiration/	3239
2	exp *Obstetric Surgical Procedures/	67285
3	exp *Antacids/	10802
4	1 and 2 and 3	14

Search strategy: H_2 antagonists

	Searches	Results
1	exp *Pneumonia, Aspiration/	3239
2	exp *Obstetric Surgical Procedures/	67285
3	exp *Histamine H2 Antagonists/	11659
4	1 and 2 and 3	16

Search strategy: Proton pump inhibitors

	Searches	Results
1	exp *Pneumonia, Aspiration/	3239
2	exp *Obstetric Surgical Procedures/	67285
3	exp Proton pump inhibitors/	14956
4	1 and 2 and 3	6

Selection of studies: Only evidence from relevant studies was included in the synthesis. These included RCTs and systematic reviews. To ensure that no primary studies were excluded, the studies cited in the respective NICE, European Society of Anaesthesiology and American Society of Anesthesiologists guidelines were likewise included in the analysis.

A 2014 Cochrane review retrieved in the literature search included most of the studies from the search and cited in the guidelines. However, the following retrieved studies were excluded from the Cochrane review:

Study	Reason
O' Sullivan	Lack of information provided to determine potential source of bias.
Qvist	Not randomised

The following discussion summarises the results of the recent Cochrane review and meta-analysis.

It was noted that the European Society of Anaesthesiology guidelines on perioperative fasting in adults and children refers to a meta-analysis[ix] comparing ranitidine to proton pump inhibitors in their effect on volume and pH of gastric fluid aspirates in the prevention of aspiration pneumonitis during general anaesthesia. However, this meta-analysis was not included as the included RCTs evaluated patients admitted for elective surgery, and not specifically pregnant women undergoing caesarean section.

Evidence synthesis:

Cochrane Review

As aspiration pneumonitis is uncommon, surrogate measure of low intragastric pH of less than 2.5 and intragastric volume greater than 25 mL were used as primary outcomes in the RCTs. However, the validity of these surrogate markers associated with the clinical outcome of aspiration pneumonitis is uncertain and based on animal studies[x]. The Cochrane review did not include the combined measure as a pre-specified outcome, but presented data on all outcomes (where available).

Effectiveness

i. Antacids versus placebo/no treatment (3 [xi] [xii] [xiii] studies, 168 women)

Primary outcomes: Compared to placebo, antacids were associated with a significantly reduce intragastric pH < 2.5 at intubation: RR 0.17, 95% CI 0.09 to 0.32, I^2= 0.0%; 2 RCTs, n=108.

Outcomes not pre- specified: There was no statistically significant difference between antacids and placebo with regards to risk of aspiration (RR 0.07, 95% CI 0.00 to 1.04, p=0.053).

ii. H_2 antagonists versus placebo/no treatment (6 [xiv] [xv] [xvi] [xvii] [xviii] [xix] studies, 385 women)

Primary outcomes: Compared to placebo, H_2 antagonists showed a significant reduction in intragastric pH < 2.5 at intubation: RR 0.09, 95% CI 0.05 to 0.18, I^2= 0.0%;2 RCTs, n=170; and reduction of intragastric volume greater than 0.4 mg/kg at intubation: RR 0.08, 95% CI 0.01 to 0.86, I^2=63%.

Outcomes not pre- specified: Statistically significant reduction in risk of aspiration at intubation with H_2 antagonists relative to placebo (RR 0.07, 95% CI 0.01to 0.33, I^2=51%). However, there was no risk reduction associated with extubation.

iii. Proton pump inhibitors (PPIs) versus placebo/no treatment (2 studies[xx] [xxi], 130 women)

Primary outcomes: Only 1 RCT (n=80) was reviewed that showed that PPIs compared to placebo was associated with a significant reduction in intragastric pH < 2.5 at intubation (RR 0.26, 95% CI 0.14 to 0.46, p < 0.00001; but no difference in reducing intragastric volume greater than 0.4 mg/kg (RR 0.46, 95% CI 0.19 to 1.09).

Outcomes not pre-specified: PPIs were associated with a statistically significant reduction in risk of aspiration versus placebo (RR 0.14, 95% CI 0.003 to 0.74, I^2=34%).

iv. Antacids versus H_2 antagonists (4 studies[xxii] [xxiii] [xxiv] [xxv], 175 women)

Primary outcomes: A statistically significant reduction in risk of pH < 2.5 at intubation was associated with antacids compared to H_2 antagonists (RR 0.07, 95% CI 0.01 to 0.52, I^2=0.0%), p < 0.00001; but no difference in reducing intragastric volume greater than 0.4 mg/kg (RR 0.46, 95% CI 0.19 to 1.09).

Outcomes not pre-specified: There was no significant difference between antacids and H2 antagonists in terms of risk reduction of aspiration (RR 1.00, 95% CI 0.018 to 5.46)

v. H_2 antagonists versus PPIs (4 studies[xxvi] [xxvii] [xxviii] [xxix], 332 women)

Primary outcomes: One RCT of 120 women undergoing elective caesarean demonstrated a greater reduction in risk of pH < 2.5 at intubation with H_2 antagonists than PPIs (RR 0.39, 95% CI 0.16 to 0.97, p = 0.042).

Outcomes not pre-specified: There was no significant difference in risk of aspiration in women undergoing elective or emergency caesarean section between H2 antagonists and PPIS (RR 0.93, 95% CI 0.20 to 4.37, I^2 = 32%)

vi. Antacids + H_2 antagonists versus placebo (1 study [xxx], 89 women)

Primary outcomes: RCT by Ormezzano *et al.* of 120 women undergoing elective caesarean demonstrated a greater reduction in risk of pH < 2.5 at intubation with H_2 antagonists combined with antacids compared to no treatment (RR 0.02, 95% CI 0.00 to 0.15, p = 0.00013).

Outcomes not pre-specified: Combination therapy also showed a significant reduction in risk of aspiration (RR 0.03, 95% CI 0.00 to 0.24, p = 0.00071))

vii. Antacids + H_2 antagonists versus antacids (2 studies[xxxi] [xxxii] 714 women)

Evidence quality: RCT by Rout *et al* (1993) was assessed to be of good quality; whilst the other RCT had methodological flaws.

Primary outcomes: RCT by Ormezzano *et al.* of 120 women undergoing elective caesarean demonstrated a greater reduction in risk of pH < 2.5 at intubation with H_2 antagonists combined with antacids versus antacids alone (RR 0.12, 95% CI 0.02 to 0.92, p = 0.041).

Outcomes not pre-specified: RCT by Rout *et al.* of 595 women undergoing emergency caesarean showed a significant reduction in risk of aspiration associated with the combination of H_2 antagonists with antacids compared to antacids alone (RR 0.11, 95% CI 0.03 to 0.46, p = 0.0027)

Effect: Reduction in risk of intragastric pH < 2.5			
Comparators	**RR**	**ARR**	**NNT**
Antacids vs placebo	RR 0.17, 95% CI 0.09 to 0.32	-0.69	2
H_2 antagonists vs placebo	RR 0.17, 95% CI 0.05 to 0.18	-0.70	2
PPIs vs placebo	RR 0.26, 95% CI 0.14 to 0.46	-0.65	2
Antacids vs H_2 antagonists	RR 0.07, 95% CI 0.01 to 0.52	-0.20	5
H_2 antagonists vs PPIs	RR 0.39, 95% CI 0.16 to 0.97	8.27	1
Antacids+H_2 antagonists vs placebo		-0.73	2
Antacids+H_2 antagonists vs antacids	RR 0.12, 95% CI 0.02 to 0.92	-0.12	9

Safety: RCTs had not assessed the potential for adverse effects.

Cochrane review mostly consists of RCTs that reviewed non-particulate antacids (e.g. sodium citrate), as it has been suggested that compared to particulate antacids (e.g. magnesium trisilicate) non-particulate antacids are less likely to cause severe pneumonitis, when aspiration with antacids occurs[xxxiii].

Evidence quality: Overall the RCTs reviewed in the Cochrane review were of poor methodological quality (in terms of sample sizes, randomisation, allocation concealment, blinding, data assessment and other potential bias). However, of the studies reviewed, the study by Rout *et al* (1993) was judged to be of better quality.

Summary:

As a single agent, antacids were shown to be relatively comparable to H_2 antagonists and PPIs in terms of reducing the risk of intragastric pH < 2.5 (though with a NNT of 2 for each intervention

to reduce intragastric pH). H_2 antagonists were associated with a reduction of intragastric volume greater than 0.4 mg/kg at intubation; PPIs showed no effect in reducing intragastric volume whilst the effect of antacids on intragastric volume has not been reported.
Combination therapy of antacids and H_2 antagonists was shown to have a greater effect in increasing intragastric pH when compared to no treatment or antacids alone. The quality of the available evidence is poor and surrogate measures have been used in the RCTS to determine the risk of aspiration pneumonitis. The validity of these surrogate measures are based on animal studies and generally accepted in practice to correlate with the risk of aspiration pneumonitis.

Sodium citrate solution has a faster onset of action than the PPI solid dosage formulations; and would possibly be of benefit in emergency Caeserean section procedures.

Aspiration as a cause of maternal mortality needs consideration and one can argue that the price of non particulate antacids as monotherapy is inexpensive[xxxiv] and available locally.

Recommendation:
A non-particulate antacid be considered for inclusion to the EML to reduce the risk of aspiration pneumonitis in patients undergoing Caeserean section.

Rationale: Antacids shown to be relatively comparable to H_2 antagonists and PPIs in terms of reducing the risk of intragastric pH < 2.5 in order to reduce the risk of aspiration pneumonitis in patients undergoing Caeserean section. Sodium citrate solution has a faster onset of action than the PPI solid dosage formulations, and would be a pragmatic option for emergency procedures. The product is available in South Africa at a current price to the public sector of R 47.82 per unit.

Level of Evidence: I Meta-analyses

References:

[i] Lewis RT, Burgess JH, Hampson LG. Cardiorespiratory studies in critical illness. Changes in aspiration pneumonitis. Arch Surg. 1971 Aug;103(2):335-40.
[ii] NICE. Caesarean section Guideline, November 2011.
[iii] Smith I, Kranke P, Murat I, Smith A, O'Sullivan G, Søreide E, Spies C, in't Veld B; European Society of Anaesthesiology. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2011 Aug;28(8):556-69.
[iv] American Society of Anesthesiologists Task Force on Obstetric Anesthesia. Practice guidelines for obstetric anesthesia: an updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. Anesthesiology. 2007 Apr;106(4):843-63.
[v] Rocke DA, Murray WB, Rout CC, Gouws E. Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. Anesthesiology 1992; 77:67–73.
[vi] Bloom SL, Spong CY, Weiner SJ, Landon MB, Rouse DJ, Varner MW, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, O'Sullivan MJ, Sibai B, Langer O, Gabbe SG; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Complications of anesthesia for cesarean delivery. Obstet Gynecol. 2005 Aug;106(2):281-7.
[vii] Republic of South Africa. Third report on confidential enquiries into maternal deaths in South Africa, 2002-2004.
[viii] Republic of South Africa. Saving Mothers 2011-2013: Sixth report on confidential enquiries into maternal deaths in South Africa.
[ix] Clark K, Lam LT, Gibson S, Currow D. The effect of ranitidine versus proton pump inhibitors on gastric secretions: a meta-analysis of randomised control trials. Anaesthesia. 2009 Jun;64(6):652-7.
[x] Roberts RB, Shirley MA. Reducing the risk of acid aspiration during cesarean section. Anesthesia and Analgesia 1974;53:859–68.
[xi] Dewan DM, Floyd HM, Thistlewood JM, Bogard TD, Spielman FJ. Sodium citrate pretreatment in elective cesarean section patients. Anesthesia and Analgesia 1985;64: 34–7.
[xii] Wig J, Biswas GC,Malhotra SK, Gupta AN. Comparison of sodium citrate with magnesium trisilicate as pre-anaesthetic antacid in emergency caesarean sections. Indian Journal of Medical Research 1987;85:306–10.
[xiii] Ormezzano X, Francois TP, Viaud JY, Bukowski JG, Bourgeonneau MC, Cottron D, et al.Aspiration pneumonitis prophylaxis in obstetric anaesthesia: comparison of effervescent cimetidine-sodium citrate mixture and sodium citrate. British Journal of Anaesthesia 1990;64:503–6.

[xiv] Iqbal MS, Ashfaque M, Akram M. Gastric fluid volume and pH: a comparison of effects of ranitidine alone with combination of ranitidine and metoclopramide in patients undergoing elective caesarean section. Annals of King EdwardMedical College 2000;6(2):189–91.
[xv] Lin CJ, Huang CL, Hsu HW, Chen TL. Prophylaxis against acid aspiration in regional anesthesia for elective cesarean section: a comparison between oral single-dose ranitidine, famotidine and omeprazole assessed with fiberoptic gastric aspiration. Acta Anaesthesiologica Sinica 1996;34(4): 179–84.
[xvi] Ozkan T, Senturk M, Yavru A, Celebi S, Pembeci K. Does preoperative fluid fasting have a benefit on aspiration prophylaxis in obstetric anaesthesia [Obstetrik anestezide preoperatif oral sivi alimi aspirasyon pnomonisi profilaksisine katki saglar mi?]. Turk Anesteziyoloji Ve Reanimasyon 2000;28:425–9.
[xvii] Tryba M, Burkert W, Husch M, Zenz M. Effectiveness of cimetidine in the prevention of aspiration pneumonia in obstetrics [Wirksamkeit von Cimetidin zur Prophylaxe der Aspirationspneumonie in der Geburtshilfe]. Fortschritte der Medizin 1983;101:1757–61.
[xviii] Zoroglu F, Karamanlioglu B, Unal C, Pamukcu Z. The value of nizatidine and famotidine in prophylaxis of aspiration pneumonia in caesarean section. British Journal of Anaesthesia 1999;82 Suppl:159–60.
[xix] Zue AS, Meye JF, Nguema PN, Nsafu DN, Milama EN. Effervescent ranitidine before urgent caesarean section: effect on gastric pH [Ranitidine effervescente avant cesarienne en urgence: effet sur le pH gastrique]. Cahiers d Anesthesiologie 1999;47:1–3.
[xx] Lin CJ, Huang CL, Hsu HW, Chen TL. Prophylaxis against acid aspiration in regional anesthesia for elective cesarean section: a comparison between oral single-dose ranitidine, famotidine and omeprazole assessed with fiberoptic gastric aspiration. Acta Anaesthesiologica Sinica 1996;34(4): 179–84.
[xxi] Ozkan T, Senturk M, Yavru A, Celebi S, Pembeci K. Does preoperative fluid fasting have a benefit on aspiration prophylaxis in obstetric anaesthesia [Obstetrik anestezide preoperatif oral sivi alimi aspirasyon pnomonisi profilaksisine katki saglar mi?]. Turk Anesteziyoloji Ve Reanimasyon 2000;28:425–9.
[xxii] Frank M, Evans M, Flynn P, Aun C. Comparison of the prophylactic use of magnesium trisilicate mixture BPC, sodium citrate mixture or cimetidine in obstetrics. British Journal of Anaesthesia 1984;56:355–61.
[xxiii] Husemeyer RP, Davenport HT. Prophylaxis for Mendelson's syndrome before elective caesarean section. A comparison of cimetidine and magnesium trisilicate mixture regimens. British Journal of Obstetrics and Gynaecology 1980;87: 565–70.
[xxiv] Ostheimer GW, Morrison JA, Lavoie C, Sepkoski C, Hoffman J, Datta S. The effect of cimetidine on the mother, newborn and neonatal neurobehavior. Anesthesiology 1982; 57:A405.
[xxv] Pickering BG, Palahniuk RJ, Cumming M. Cimetidine premedication in elective caesarean section. Canadian Anaesthetists Society Journal 1980;27:33–5.
[xxvi] Yau G, Kan AF, Gin T, Oh TE. A comparison of omeprazole and ranitidine for prophylaxis against aspiration pneumonitis in emergency caesarean section. Anaesthesia 1992;47:101–4.
[xxvii] Tripathi A, Somwanshi M, Singh B, Bajaj P. A comparison of intravenous ranitidine and omeprazole on gastric volume and ph in women undergoing emergency caesarean section. Canadian Journal of Anaesthesia 1995;42(9):797–800.
[xxviii] Lin CJ, Huang CL, Hsu HW, Chen TL. Prophylaxis against acid aspiration in regional anesthesia for elective cesarean section: a comparison between oral single-dose ranitidine, famotidine and omeprazole assessed with fiberoptic gastric aspiration. *Acta Anaesthesiologica Sinica* 1996;34(4): 179–84.
[xxix] Ewart MC, Yau G, Gin T, Kotur CF, Oh TE. A comparison of oral omeprazole and ranitidine as premedication for elective caesarean section. Proceedings of Spring Meeting of Obstetric Anaesthetists Association; 1990; London, UK. 1990:33.
[xxx] Ormezzano X, Francois TP, Viaud JY, Bukowski JG, Bourgeonneau MC, Cottron D, et al.Aspiration pneumonitis prophylaxis in obstetric anaesthesia: comparison of effervescent cimetidine-sodium citrate mixture and sodium citrate. British Journal of Anaesthesia 1990;64:503–6.
[xxxi] Ormezzano X, Francois TP, Viaud JY, Bukowski JG, Bourgeonneau MC, Cottron D, et al.Aspiration pneumonitis prophylaxis in obstetric anaesthesia: comparison of effervescent cimetidine-sodium citrate mixture and sodium citrate. British Journal of Anaesthesia 1990;64:503–6.
[xxxii] Rout CC, Rocke DA, Gouws E. Intravenous ranitidine reduces the risk of acid aspiration of gastric contents at emergency cesarean section. Anesthesia & Analgesia 1993; 76:156–61.
[xxxiii] Gibbs CP, Schwartz DJ, Wynne JW, Hood CI, Kuck EJ. Antacid pulmonary aspiration in the dog. Anesthesiology 1979;51:380–5.
[xxxiv] Email communication from Obsdian Health, 9 September 2015. Price per 25 mL bottle containing sodium citrate dihydrate 2,5 g and citric acid monohydrate 1,65 g = R 47.82.