Kliiniline küsimus nr 5

Kas kõikide ähvardavate enneaegsete sünnituste korral tuleb enneaegse vastsündinu ravitulemi parandamiseks manustada magneesiumsulfaati ühekordse kuurina võrreldes korduva kuurina võrreldes mitte manustamisega?
Kriitilised tulemusnäitajad: ema terviseseisund, lapse peamised tulemusnäitajad

Ravijuhendid

Soovitused neuroprotektsiooni kohta on antud kolmes ravijuhendis: kahes Austraalia (NHRMC 2010, Queensland CG 2014) ja ühes Kanada juhendis (SOGC 2011). Soovitused põhinevad viiel randomiseeritud kontrolluuringul (need uuringud on kaasatud ka käesoleva juhendi kontekstis käsitletud kolmes süstemaatilises ülevaates). Juhendid olid hinnatud AGREE meetodiga. Austraalia juhendid said kõrge hinnangu, Kanada juhendi hinnang oli madalam, kuna puudus piisavalt infot juhendi koostamismetoodika kohta. Tõenduspõhised allikad on kõikides juhendites samad.

Neuroprotektiivset ravi magneesiumsulfaadiga soovitatakse kasutada ähvardava enneaegse sünnituse korral, kuna see vähendab riski eelkõige tserebraalparalüüsiks (A).

Ravi soovituslik algusaeg gestatsioonivanust arvestades on ≤30 nädalat Austraalia juhendites (B) ja ≤32 nädalat Kanada juhendis (B).

Ravi soovituslik algus on 24 tundi enne oodatavat sünnitust või 4 tundi enne planeeritavat sünnitust (B). /Magee, L., Sawchuck, D., Synnes, A., von Dadelszen, P., 2011. SOGC Clinical Practice Guideline. Magnesium sulphate for fetal neuroprotection. J Obstet Gynaecol Can 33, 516–529./ .//

Doosiks soovitatakse 4 g boolusena 20–30 min jooksul ja edasi 1g tunnis kuni sünnituseni või maksimaalselt 24 tunni jooksul (C).

Erakorralises situatsioonis (loote distress või naisel verejooks) ei tohi olla magneesiumsulaadi manustamine erakorralise abiga viivitamise põhjuseks.

Kui sünnitus ei toimu 24 tunni jooksul pärast ravi alustamist ja enneaegse sünnituse oht tekib raseduse ajal hilisemalt uuesti, võib magneesiumsulaadi manustamist taas kaaluda (C).

Neuroprotektsiooni soovitatakse sõltumata sellest, kas tegemist on üksik- või mitmikrasedusega, sõltumata enneaegse sünnituse põhjusest, naise eelnevate sünnituste arvust ja sünnituse viisist (B).

Rasedaid, kes saavad magneesiumsulfaadi neuroprotektsiooni eesmärgil, soovitatakse monitoorida kõrvaltoimete suhtes analoogselt nende rasedatega, kes saavad sama ravi preeklampsia korral ekampsia ära hoidmiseks (C). /Magee, L., Sawchuck, D., Synnes, A., von Dadelszen, P., 2011. SOGC Clinical Practice Guideline. Magnesium sulphate for fetal neuroprotection. J Obstet Gynaecol Can 33, 516–529.

Süstemaatilised ülevaated

Antud teema kohta on läbi viidud 5 randomiseeritud kontrolluuringut ja nende põhjal on tehtud 3 metaanalüüsi erinevate autorite poolt.
Nelja randomiseeritud uuringu esmaseks eesmärgiks oli ananüüsida magneesiumsulfaadi neuroprotektiivset toimet enneaegsele vastsündinule. (2002 Mittendorf, 2003 Crowther, 2007 Marret ja 2008 Rouse et al.) Viienda uuringu (Duley et al 2006) esmaseks eesmärkiks oli magneesiumsulfaadi mõju ema tervisele, kui seda kasutati eklampsia preventsiooniks ja neuroprotektiivne mõju vastsündinule oli sekundaarseks eesmärgiks. Tuleks mainida, et kõikidesse metaanalüüsidesse oli kaasatud Mittendorf 2002 randomiseeritud kontrolluuring, kus tulemused olid teistest erinevad ja raporteeriti magneesiumi kahju vastsündinu tulemusnäitajatele. Antud uuring on vastuolus kõigi teste suuremate uuringutega. Uuringu kvaliteet on hinnatud madalaks. Põhjuseks on väike osalejate arv uuringus (ainult 29 ema (30 last) said MgSO4 neuroprotekstiooni eesmärgil ja 46 ema (55 last) tokolüüsi eesmärgil), randomiseerimise meetod ei ole kirjeldatud, tokolüüsi osa ei olnud pime ja neuroprotektiivne osa oli. Põhilised tulemusnäitajad olid vastsündinu intraventrikulaarne hemorraagia ja surm, mitte tserebraalparalüüs.

Metaanalüüside tulemused on sarnased ja üldine järeldus kinnitab, et magneesiumsulfaadi manustamine ähvardava enneaegse sünnituse puhul gestatsiooni vanuses ≤ 32-34 vähendab eelkõige tserebraalparalüüsi teket vastsündinul ja ei tõsta perinataalse suremuse riski.
Efekt on suurem sügavalt enneaegsetel vastsündinutel, kes on sündinud ≤ 32 nädalat. Magneesiumsulfaadi manustamine ei ole seotud tõsiste kõrvaltoimetega ei emale ega vastsündinule.

Kõige mahukam süstemaatiline ülevaade (Cochrane review) oli publitseeritud Doyle LW et al poolt 2009 aastal. Ülevaate eesmärgiks oli uurida magneesiumsulfaati neuroprotektiivset toimet vastsündinule, kelle ema sai ravi ähvardava enneaegse sünnituse tõttu. Primaarseteks tulemusnäitajateks olid neonataalne suremus ja tserebraalparalüüsi esinemissagedus. Analüüsi oli kaasatud 5 randomiseeritud kontrolluuringut, mis hõlmasid kokku 6145 vastsündinut. Enamik kaasatud vastsündinutest olid sündinud vanuses alla 34 rasedusnädalat vastavalt uuringu protokollidele, kuid ühest uuringust oli kaasatud 788 vastsündinut vanuses 34-36 rasedusnädalat.
Autorid järeldasid, et magneesiumsulfaat langetab tserebraalparalüüsi üldist tekke riski enneaegsel vastsündinul (RR 0.68 95% CI 0.54-0.87). Samuti oli täheldatav oluline langus #gross motor dysfuntion# esinemissageduses - RR 0.61 (95% CI 0.44-0.85).
NNT (number needed to treat), et ennetada 1 tserebraalparalüüsi juht, oli 63(95% CI 45-155). Mõju suremuse vähendamisele ei täheldatud ja see oli analoogne magneesiumsulfaati *versus* platseebo-rühmas (RR 1.01; 95% CI 0.82–1.23).
Mis puudutab kõrvaltoimeid emadel, siis magneesiumsulfaat oli seotud väiksemate kõrvaltoimetega nagu kuumad hood, iiveldus, higistamine ja lokaalne ärritus infusiooni piirkonnas. Raskeid kõvaltoimeid nagu südameseiskus, respiratoorne depressioon, kopsuturse, massiivne sünnitusjärgne verejooks, ei esinenud.

Teine süstemaatiline ülevaade, mis oli tehtud Conde-Agudelo et al poolt, analüüsis spetsiifiliselt magnesiumsulfaadi neuroprotektiivset toimet vastsündinule

gestatsioonivanuses alla 34 rasedusnädalat. Analüüsi oli kaasatud samad 5 randomiseeritud kontrolluuringut, mis hõlmasid kokku 5357 vastsündinud (võrreldes Doyle ülevaatega olid välja jäetud vastsündinud gestatsioonivanuses üle 34 nädala – n=788). Esmased tulemusnäitajad olid tserebraalparalüüsi esinemine vastsündinul ja suremus (varajane neonataalne suremus ja suremus kuni 2 eluaastat).
Autorid said sarnase tulemuse analüüsides gestatsioonivanust alla 34 nädalat, et magneesiumsulfaat vähendab üldist riski tserebraalparalüüsi tekkeks (RR **0.69**; 95% confidence interval [CI], 0.55-0.88), eraldi vähendab riski keskmise ja raske astme tserebraalparalüüsi tekeks (RR, **0.64**; 95% CI, 0.44-0.92) ja vähendab #substantial gross motor dysfunction# (RR, **0.60**; 95% CI, 0.43-0.83). Suremuses oli analoogne mõlemas rühmas (RR, **1.01**; 95% CI, 0.89-1.14).Väiksemad kõrvaltoimed oli täheldatud naistel magneesiumsulfaadi rühmas. NNT (number needed to treat), et ennetada 1 tserebraalparalüüsi juht, oli 52 (95% CI 31-154).
Ülevaate raames tegid autorid ka kulu-efektiivsuse analüüsi ja järeldasid, et magneesiumsulfaadi manustamine neuroprotektsiooni eesmärgiga alla 34 nädalat on kulu-efektiivne interventsioon.

Kulu-efektiivsuse analüüs antud teema kohta on publitseeritud ka kanada autorite poolt: Celeste D Bickfor et al poolt 2013 aastal - magneesiumsulfaadi manustamine neuroprotektsiooni eesmärgiga ähvardava enneaegse sünnituse korral alla 32 nädalat on kulu-efektiivne interventsioon tervishoiu süsteemile.

Kolmas metaanalüüs oli publitseeritud Maged M. Costantine et al poolt.
Analüüsi oli kaasatud 5 randomiseeritud kontrolluuringut, kokku 5235 vastsündinut.
Statistilised analüüsid olid läbi viidud eraldi erinevates gestatsioonivanuse rühmades: alla 32-34 ja alla 30 nädalat. Tulemused olid analoogsed eelnevalt mainitud ülevaadetega. Statistiliselt parimad tulemised oli näidatud rühmas alla 30 nädalat.
NNT: 46 alla 30 nädalat ja 56 32-34 nädalat.

Uuematest uuringutest on Doyle poolt publitseeritud randomiseeritud kontrolluuring magneesiumsulfaadi mõjust lastele koolieas. (2014)
Uuringu eemärgiks oli uurida neuroloogilisi, kognitiivseid, käitumuslikke ja akadeemilisi tulemusi koolieas nendel lastel, kelle emale oli manustatud magneesiumsulfaati ähvardava enneaegse sünnituse puhul vastsündinud neuroprotektsiooni eesmärgil.
Aluseks oli võetud 2003. aastal Crowther et al. (ACTOMgSO4) uuring, kus osales 1062 naist (1225 loodet) raseduse suuruses alla 30 nädalat.
Uuringus osalenud vastsündinud olid üle vaadatud lapse eas 6 ja 11 aasta vanuselt.
1225 vastsündinust oli elus 867 ja nendest 669 (77%) osalesid hilisemas analüüsis. Rühmade vaheline erinevus muude tunnuste poolest väga minimaalne.
Tulemused olid sarnased mõlemas grupis, kuid suremus oli veidi väiksem magneesiumsulfaadi grupis. On vajalikumad suuremad uuringud, et tõestada looteeas magneesiumsulfaadi manustamise kasulikkus hilisemas elus.

2014. aastal publitseeritud ES Bain et al poolt IRIS randomiseeritud kontrolluuring, mille eesmärgiks oli uurida magnesiumsulfaadi infusioonikiiruse mõju kõrvaltoimetele emal. Uuringus osales 51 naist, kes randomiseeriti kahte rühma. Üks rühm sai

magneesiumsulfaati 4 g 20 min jooksul ja teine 60 min jooksul. Järelduseks toodi välja, et aeglasem infusioonikiirus ei vähendanud kõrvaltoimete esinemissagedust emadel. Uuritavate arv oli väike.

Vaatamata olemasolevatele uuringutele, jäävad siiski mõned vastamata küsimused.
Milline gestatsiooniaeg peaks olema *cut–off*? Milline doos ja režiim on kõige efektiivsem ja tekitb kõige vähem kõrvaltoimeid emal? Kas korduv manustamine on vajalik?

Käigusolevad uuringud, mis aitavad küsimustele vastata:
Antenatal magnesium individual participant data international collaboration: assessing the benefits for babies using the best level of evidence (**AMICABLE**) – eesmärgid: uurida optimaalset gestatsiooniaega; ajalist kriteeriumi, millal manustada; milline doos ja reziim.

ARCH (Australian Research Center) alustas (**MAGENTA)** randomideeritud topeltpimeda kontrolluuringut, et spetsiifiliselt vaadata neuroprotektsiooni kasu 30-34 rasedusnädalal. Uuringu tulemusi saab kaasata olemasolevatesse metaanalüüsidesse.

Magnesium Sulphate for Preterm Birth (**MASP** Study) Lene Huusom, Hvidovre University Hospital Denmark trial. Uus käigusolev randomiseeritud kontrolluuring magneesiumsulfaadi neuroprotektsiivsest mõjust enneaegsele vastsündinule. Tulemused saab kaasata metaanalüüsidesse. Tulemusi on oodata detsembris 2016 aastal.

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Five trials (6145 babies) were eligible for this review. Antenatal magnesium sulphate therapy given to women at risk of preterm birth substantially reduced the risk of cerebral palsy in their child (relative risk (RR) 0.68; 95% Confidence interval (CI) 0.54 to 0.87; five trials; 6145 infants). There was also a significant reduction in the rate of substantial gross motor dysfunction (RR 0.61; 95% CI 0.44 to 0.85; four trials; 5980 infants). No statistically significant effect of antenatal magnesium sulphate therapy was detected on paediatric mortality (RR 1.04; 95% CI 0.92 to 1.17; five trials; 6145 infants), or on other neurological impairments or disabilities in the first few years of life. Overall there were no significant effects of antenatal magnesium therapy on combined rates of mortality with cerebral palsy, although there were significant reductions for the neuroprotective groups RR 0.85; 95% CI 0.74 to 0.98; four trials; 4446 infants, but not for the other intent subgroups. There were higher rates of minor maternal side effects in the magnesium groups, but no significant effects on major maternal complications. The neuroprotective role for antenatal magnesium sulphate therapy given to women at risk of preterm birth	Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. *Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Database Syst Rev* 2009;(1): CD004661.

for the preterm fetus is now established. The number of women needed to be treated to benefit one baby by avoiding cerebral palsy is 63 (95% confidence interval 43 to 155). Given the beneficial effects of magnesium sulphate on substantial gross motor function in early childhood, outcomes later in childhood should be evaluated to determine the presence or absence of later potentially important neurological effects, particularly on motor or cognitive function.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

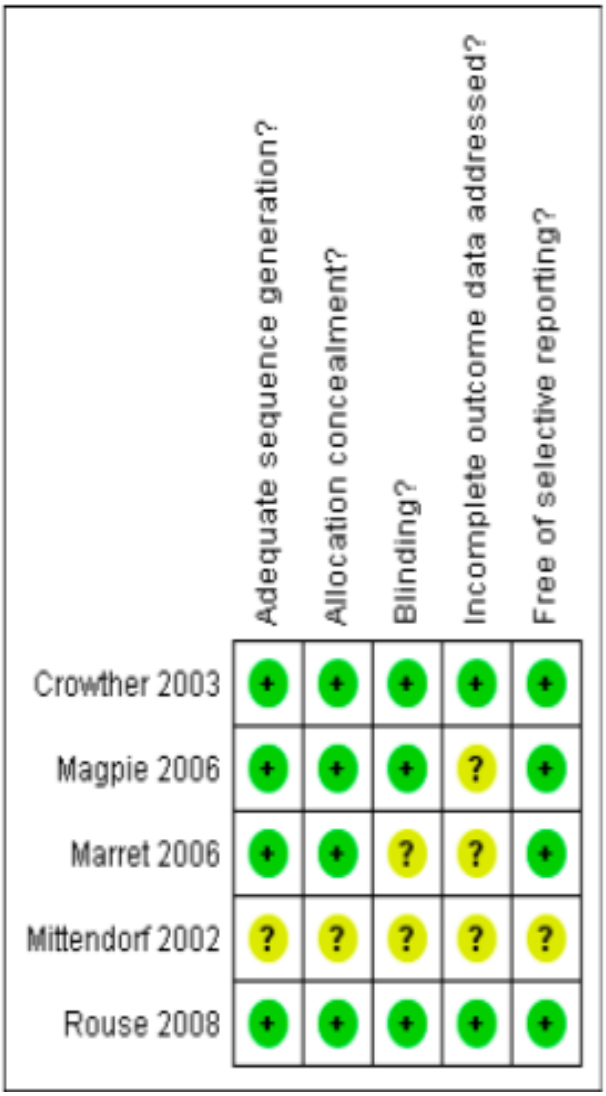


Table 1. Characteristics of Included Studies

Study (First Author)	Inclusions	Women (n)	Fetuses (n)	Magnesium Dose
MagNET (Mittendorf et al[17])	25–33 wk in preterm labor	149	165	Tocolytic arm; 4 g loading, 2–3 g/h maintenance. Neuroprotective arm; 4 g loading only
ACTOMgSO$_4$ (Crowther et al[18])	<30 wk, likely to deliver within 24 h	1,062	1,255	4 g loading, 1 g/h maintenance
MAGPIE (Duley et al[22,23])	All gestations* with severe preeclampsia	1,544*	1,593*	4 g loading, 1 g/h IV maintenance, or 5 g every 4 h IM
PREMAG (Marret et al[19])	<33 wk of gestation in labor	573	688	4 g loading only
BEAM (Rouse et al[13])	24–31 wk at high risk of spontaneous birth	2,241	2,444	6 g loading, 2 g/h maintenance

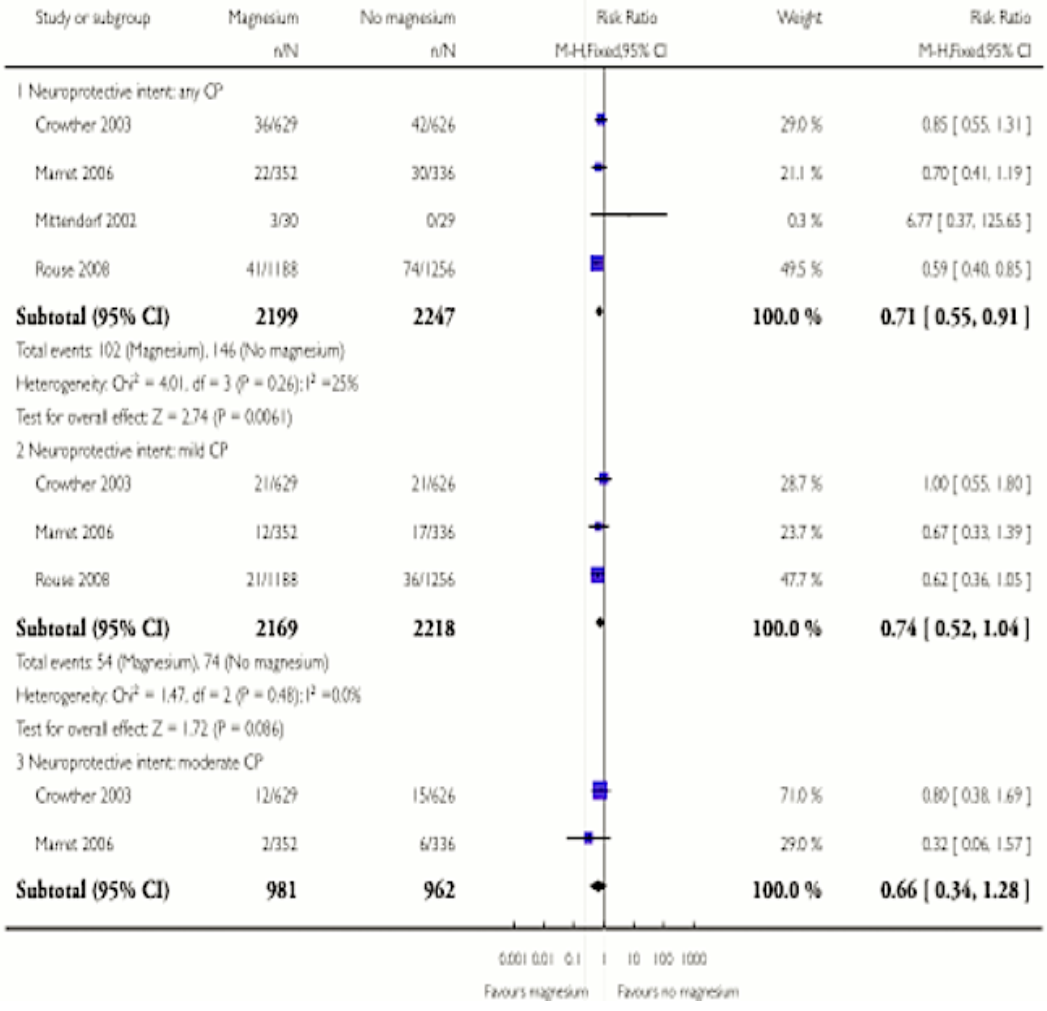
MagNET, Magnesium and Neurologic Endpoints Trial; ACTOMgSO$_4$, Australasian Collaborative Trial of Magnesium Sulphate. MAGPIE, Magnesium Sulphate for Prevention of Eclampsia; IV, intravenously; IM, intramuscularly; BEAM, Beneficial Effects of Antenatal Magnesium Sulfate.
* Only less than 37 weeks and undelivered at enrolment included in this analysis.

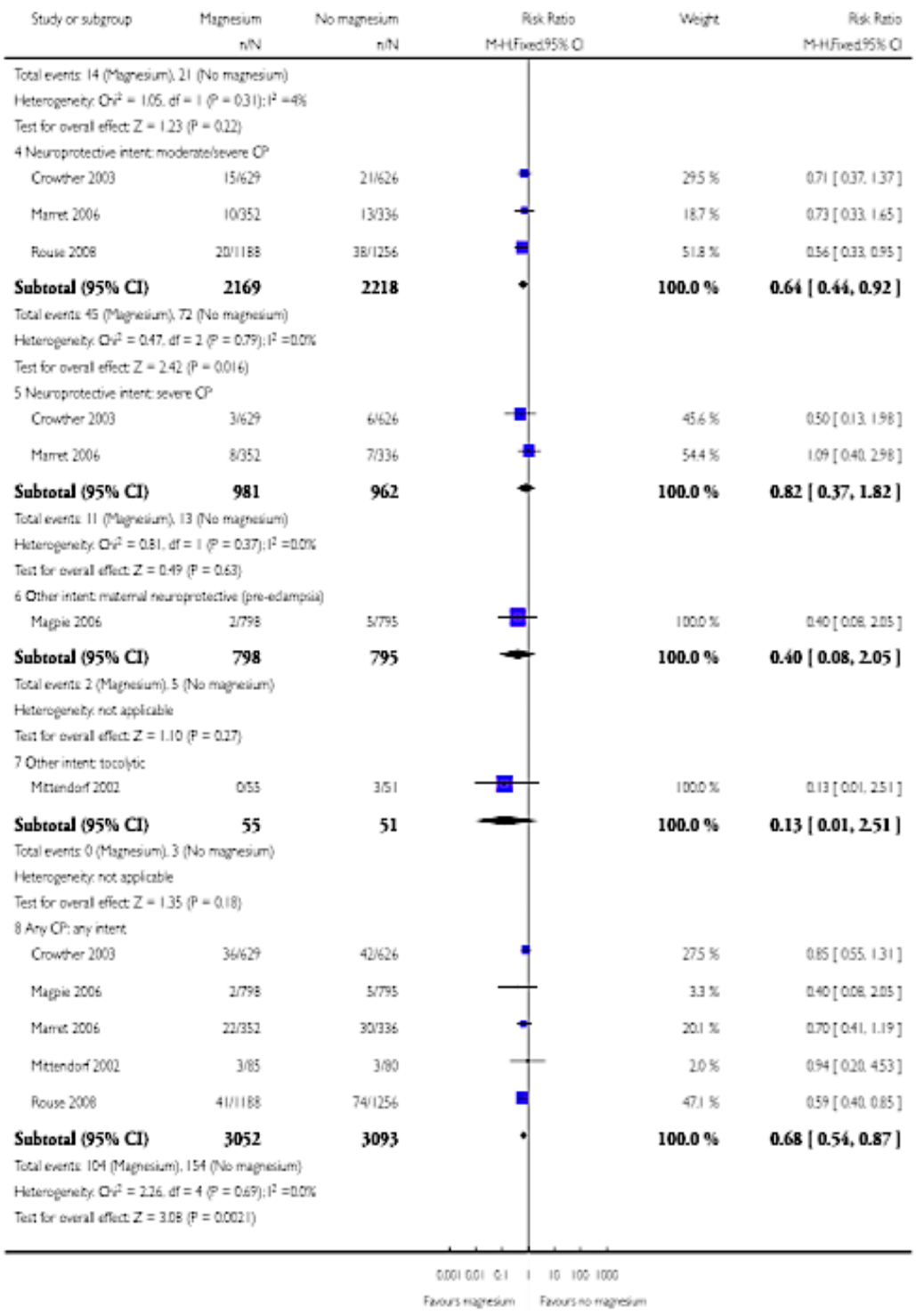
Analysis 1.4. Comparison 1 Magnesium versus no magnesium, Outcome 4 Cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 4 Cerebral palsy




Study or subgroup
Magnesium n/N
No magnesium n/N
Risk Ratio M-H,Fixed,95% CI
Weight
Risk Ratio M-H,Fixed,95% CI
Total events: 14 (Magnesium), 21 (No magnesium)
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² =4%
Test for overall effect: Z = 1.23 (P = 0.22)
4 Neuroprotective intent: moderate/severe CP
Crowther 2003 15/629 21/626 29.5 % 0.71 [0.37, 1.37]
Marret 2006 10/352 13/336 18.7 % 0.73 [0.33, 1.65]
Rouse 2008 20/1188 38/1256 51.8 % 0.56 [0.33, 0.95]
Subtotal (95% CI) 2169 2218 100.0 % 0.64 [0.44, 0.92]
Total events: 45 (Magnesium), 72 (No magnesium)
Heterogeneity: Chi² = 0.47, df = 2 (P = 0.79); I² =0.0%
Test for overall effect: Z = 2.42 (P = 0.016)
5 Neuroprotective intent: severe CP
Crowther 2003 3/629 6/626 45.6 % 0.50 [0.13, 1.98]
Marret 2006 8/352 7/336 54.4 % 1.09 [0.40, 2.98]
Subtotal (95% CI) 981 962 100.0 % 0.82 [0.37, 1.82]
Total events: 11 (Magnesium), 13 (No magnesium)
Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² =0.0%
Test for overall effect: Z = 0.49 (P = 0.63)
6 Other intent: maternal neuroprotective (pre-eclampsia)
Magpie 2006 2/798 5/795 100.0 % 0.40 [0.08, 2.05]
Subtotal (95% CI) 798 795 100.0 % 0.40 [0.08, 2.05]
Total events: 2 (Magnesium), 5 (No magnesium)
Heterogeneity: not applicable
Test for overall effect: Z = 1.10 (P = 0.27)
7 Other intent: tocolytic
Mittendorf 2002 0/55 3/51 100.0 % 0.13 [0.01, 2.51]
Subtotal (95% CI) 55 51 100.0 % 0.13 [0.01, 2.51]
Total events: 0 (Magnesium), 3 (No magnesium)
Heterogeneity: not applicable
Test for overall effect: Z = 1.35 (P = 0.18)
8 Any CP: any intent
Crowther 2003 36/629 42/626 27.5 % 0.85 [0.55, 1.31]
Magpie 2006 2/798 5/795 3.3 % 0.40 [0.08, 2.05]
Marret 2006 22/352 30/336 20.1 % 0.70 [0.41, 1.19]
Mittendorf 2002 3/85 3/80 2.0 % 0.94 [0.20, 4.53]
Rouse 2008 41/1188 74/1256 47.1 % 0.59 [0.40, 0.85]
Subtotal (95% CI) 3052 3093 100.0 % 0.68 [0.54, 0.87]
Total events: 104 (Magnesium), 154 (No magnesium)
Heterogeneity: Chi² = 2.26, df = 4 (P = 0.69); I² =0.0%
Test for overall effect: Z = 3.08 (P = 0.0021)
0.001 0.01 0.1 1 10 100 1000
Favours magnesium
Favours no magnesium

Five RCTswere included (5,235 fetuses/ infants). When analyzed by GA at randomization, in utero exposure to magnesium sulfate at less than 32–34 weeks did not reduce the rate of death or cerebral palsy (relative risk [RR] 0.92, 95% confidence interval [CI] 0.83–1.03). However, cerebral palsy (RR 0.70, 95% CI 0.55–0.89), moderate-severe cerebral palsy (RR 0.60, 95% CI 0.43–0.84), and death or moderate-severe cerebral palsy were significantly reduced, without an evident increase in the risk of death (RR 1.01, 95% CI 0.89–1.14). Similar results were obtained when the GA at randomization was < 30 weeks. When only neuroprotection trials (4 trials, 4324 fetuses/infants) are analyzed, in utero exposure to magnesium sulfate additionally reduced the primary outcome of death or cerebral palsy. The number needed to treat to prevent one case of cerebral palsy among those who survive until age 18–24 months is 46 in infants exposed to magnesium sulfate in utero before 30 weeks, and 56 in infants exposed to magnesium sulfate in utero before 32 to 34 weeks (95% confidence limits 26–187). Fetal exposure to magnesium sulfate in women at risk for preterm delivery significantly reduces the risk of cerebral palsy without increasing the risk of death.	Costantine MM, Weiner SJ, Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Effects of antenatal exposure to magnesium sulfate on neuroprotection and mortality in preterm infants: a meta-analysis. Obstet Gynecol* 2009; 114:354–64.
Systematic review and metaanalysis of randomized controlled trials to determine whether magnesium sulfate administered to women at risk of preterm delivery before 34 weeks of gestation may reduce the risk of cerebral palsy in their children. Six trials involving 4796 women and 5357 infants were included. Antenatal magnesium sulfate was associated with a significant reduction in the risk of cerebral palsy (relative risk [RR], 0.69; 95% confidence interval [CI], 0.55-0.88), moderate or severe cerebral palsy (RR, 0.64; 95% CI, 0.44-0.92), and substantial gross motor dysfunction (RR, 0.60; 95% CI, 0.43-0.83). There was no overall difference in the risk of total pediatric mortality (RR, 1.01; 95% CI, 0.89-1.14). Minor side effects were more frequent among women receiving magnesium sulfate. In conclusion, magnesium sulfate administered to women at risk of delivery before 34 weeks of gestation reduces the risk of cerebral palsy.	Conde-Agudelo A, Romero R. *Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: a systematic review and metaanalysis. Am J Obstet Gynecol* 2009; 200:595–609.

TABLE 2
Modified Jadad score for assessment of methodologic quality of included studies

	Mittendorf et al[29,30]					
Item	Tocolytic arm	Neuroprotective arm	Crowther et al[31]	Magpie group[32]	Marret et al[33,34]	Rouse et al[35]
Randomization	Yes	Yes	Yes	Yes	Yes	Yes
Method to generate randomization clear and appropriate	Yes	Yes	Yes	Yes	Yes	Yes
Double blind	No	Yes	Yes	Yes	Yes	Yes
Methods for blinding appropriate	No	Yes	Yes	Yes	Yes	Yes
Method of allocation concealment[a]	No	Unreported	Adequate	Adequate	Adequate	Adequate
Description of withdrawal or dropout	No	No	Yes	Yes	Yes	Yes
Completeness of follow-up of randomized fetuses (%)[b]	Unreported	Unreported	98.9	47.4[c]	98.5	95.6
Total score	2	4	8	7	8	8

Yes = 1 point; no = zero points; scores: 0 = lowest quality, 8 = highest quality.

[a] Adequate = 2 points; no concealment of allocation or inadequate method or unreported = zero points; [b] follow-up ≥ 95% = 1 point; follow-up < 95% or unreported = zero points; [c] for fetuses of all gestational ages and undelivered at randomization.

Conde-Agudelo. Antenatal magnesium sulfate for preventing cerebral palsy in preterm infants. Am J Obstet Gynecol 2009.

TABLE 3
Effect of magnesium sulfate on cerebral palsy and pediatric mortality

		No. of events/total number			
Outcome	No. of trials	Magnesium	No magnesium	Relative risk (95% CI)	I^2 (%)
Cerebral palsy	6[30-32,34,35]	104/2658	152/2699	0.69 (0.55-0.88)	4.4
Moderate/severe cerebral palsy	3[31,34,35]	45/2169	72/2218	0.64 (0.44-0.92)	0.0
Mild cerebral palsy	3[31,34,35]	54/2169	74/2218	0.74 (0.52-1.04)	0.0
Total pediatric mortality	6[29,31,32,34,35]	401/2658	400/2699	1.01 (0.89-1.14)	38.9
Fetal mortality	5[29,31,34,35]	17/2254	22/2298	0.78 (0.42-1.46)	0.0
Under 2 y of corrected age mortality	5[29,31,34,35]	217/2254	220/2298	1.00 (0.84-1.19)	47.3
Death or cerebral palsy	6[30-32,34,35]	505/2658	551/2699	0.92 (0.83-1.02)	43.3

CI, confidence interval.

Conde-Agudelo. Antenatal magnesium sulfate for preventing cerebral palsy in preterm infants. Am J Obstet Gynecol 2009.

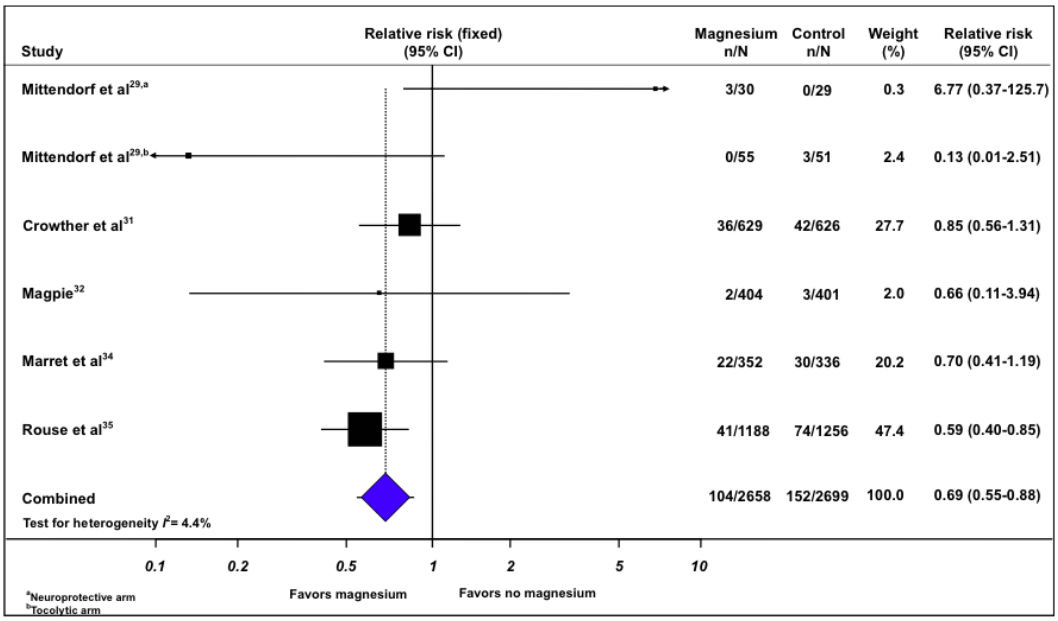


FIGURE 2
Effect of magnesium sulfate on cerebral palsy

Conde-Agudelo. Antenatal magnesium sulfate for preventing cerebral palsy in preterm infants. Am J Obstet Gynecol 2009.

Cost-effectivness analysis of the study.

The United Cerebral Palsy Foundation has estimated that about 8000 infants are diag- nosed with cerebral palsy each year in the United States of which about 25% (n 2000) are born before 34 weeks of gesta- tional age.Therefore, if all women who deliver before 34 weeks of gestation receive antenatal magnesium sulfate, the esti- mated number of new cases of cerebral palsy that hypothetically could be pre- vented annually is 620 (95% CI, 240-900). The number of women at risk of pre- term delivery before 34 weeks of gestation who needed to receive magnesium sulfate to prevent 1 case of cerebral palsy was 52 (95% CI, 31-154). A recent cost decision analysis from the United States revealed that the total cost for administrating magnesium sulfate as a tocolytic agent, including costs attributable to the evaluation and treatment of its adverse events, was $197.90 per patient in 2005. Thus, if magnesium sulfate was given to all women at risk of preterm de- livery before 34 weeks of gestation, the incremental cost of preventing one case of cerebral palsy would be $10,291 (95% CI, 6135-30,477).

Study was desined to evaluate a slower (compared with a standard) infusion rate of the loading dose of magnesium sulphate for preterm fetal neuroprotection as a strategy to reduce maternal adverse effects, 51 women at <30 weeks of gestation, where birth was planned or expected within 24 hours were involved. Women received a loading infusion of 4 g of magnesium sulphate over either 60 or 20 minutes (followed by maintenance of 1 g/hour until birth, or for up to 24 hours). Overall, 71% of women experienced adverse effects during the first hour of their infusion; the difference between groups was not significant [15/25 (60%) 60-minute loading; 21/26 (81%) 20-minute loading; risk ratio (RR) 0.74; 95% confidence interval (95% CI) 0.51–1.08]. Although no serious maternal complications occurred, adverse effects led to three women ceasing the loading treatment (1/25 in the 60-minute loading group; 2/26 in the 20-minute loading group; RR 0.52; 95%	ES Bain, PF Middleton, LN Yelland, PJ Ashwood, CA Crowther *Maternal adverse effects with different loading infusion rates of antenatal magnesium sulphate for*

<table>
<tr>
<td>CI 0.05–5.38). Women in the 60-minute loading group experienced significantly less warmth and flushing at 20 minutes into the infusion (7/25 in the 60-minute loading group; 15/26 in the 20-minute loading group; RR 0.49; 95% CI 0.24–0.99). No other differences between groups for maternally reported and clinical adverse effects were shown. A slower rate of administering the loading dose of magnesium sulphate did not reduce the occurrence of maternal adverse effects overall. Flushing and warmth at 20 minutes into the infusion was reduced with a slower infusion.</td>
<td>preterm fetal neuroprotection: the IRIS randomised trial.

BJOG. 2014 Apr;121(5):595-603</td>
</tr>
<tr>
<td>Antenatal magnesium sulfate given to pregnant women at imminent risk of very preterm delivery reduces the risk of cerebral palsy in early childhood, although its effects into school age have not been reported from randomized trials. Study was desined to determine the association between exposure to antenatal magnesium sulfate and neurological, cognitive, academic, and behavioral outcomes at school age. The ACTOMgSO4 (2003 Crowther et al) was a randomized clinical trial conducted in 16 centers in Australia and New Zealand, comparing magnesium sulfate with placebo given to pregnant women (n = 535 magnesium; n = 527 placebo) for whom imminent birth was planned or expected before 30 weeks' gestation. Children who survived from the 14 centers who participated in the school-age follow-up (n = 443 magnesium; n = 424 placebo) were invited for an assessment at 6 to 11 years of age between 2005 and 2011. There were 1255 fetuses known to be alive at randomization. Of 867survivors available for follow-up, outcomes at school age (corrected age 6-11 years) were determined for 669 (77%). There was little difference between groups on any of the cognitive, behavioral, growth, or functional outcomes.
<table>
<tr><th rowspan="2">Outcomes at School Age</th><th colspan="2">No./Total No. (%)</th><th rowspan="2">Comparison (95% CI)</th><th rowspan="2">P Value</th></tr>
<tr><th>Magnesium Sulfate Group</th><th>Placebo Group</th></tr>
<tr><td>Mortality</td><td>88/629 (14)</td><td>110/626 (18)</td><td>RR, 0.80 (0.62-1.03)</td><td>.08</td></tr>
<tr><td>Cerebral palsy</td><td>23/295 (8)</td><td>21/314 (7)</td><td>OR, 1.26 (0.84-1.91)</td><td>.27</td></tr>
<tr><td>Abnormal motor function</td><td>80/297 (27)</td><td>80/300 (27)</td><td>OR, 1.16 (0.88-1.52)</td><td>.28</td></tr>
</table>
Magnesium sulfate given to pregnant women at imminent risk of birth before 30 weeks' gestation was not associated with neurological, cognitive, behavioral, growth, or functional outcomes in their children at school age, although a mortality advantage cannot be excluded. The lack of long-term benefit requires confirmation in additional studies.</td>
<td>Lex W. Doyle, MD, MSc; Peter J. Anderson, PhD; Ross Haslam, MBBS; Katherine J. Lee, PhD; Caroline Crowther, MD.

School-age outcomes of very preterm infants after antenatal treatment with magnesium sulfate vs placebo.

JAMA. 2014 Sep 17;312(11):1105-13</td>
</tr>
</table>

The aim of this study was to assess the cost-effectiveness of administering magnesium sulphate to patients in whom preterm birth at < 32^{+0} weeks gestation is either imminent or threatened for the purpose of fetal neuroprotection. Multiple decision tree models and probabilistic sensitivity analyses were used to compare the administration of magnesium sulphate with the alternative of no treatment. Two separate cost perspectives were utilized in this series of analyses: a health system and a societal perspective. In addition, two separate measures of effectiveness were utilized: cases of cerebral palsy (CP) averted and quality-adjusted life years (QALYs). From a health system and a societal perspective, respectively, a savings of $2,242 and $112,602 is obtained for each QALY gained and a savings of $30,942 and $1,554,198 is obtained for each case of CP averted when magnesium sulphate is administered to patients in whom preterm birth is imminent. From a health system perspective and a societal perspective, respectively, a cost of $2,083 is incurred and a savings of $108,277 is obtained for each QALY gained and a cost of $28,755 is incurred and a savings of $1,494,500 is obtained for each case of CP averted when magnesium sulphate is administered to patients in whom preterm birth is threatened. Administration of magnesium sulphate to patients in whom preterm birth is imminent is a dominant (i.e. cost-effective) strategy, no matter what cost perspective or measure of effectiveness is used. Administration of magnesium sulphate to patients in whom preterm birth is threatened is a dominant strategy from a societal perspective and is very likely to be cost-effective from a health system perspective.	Bickford CD, Magee LA, Mitton C, Kruse M, Synnes AR, Sawchuck D, Basso M, Senikas VM, von Dadelszen P; MAG-CP Working Group. *Magnesium sulphate for fetal neuroprotection: a cost-effectiveness analysis.* *BMC Health Serv Res. 2013 Dec 19;13:527. doi: 10.1186/1472-6963-13-527.*

Otsingu strateegia.

Andmebaas	Medline (PUBMED)
Otsingustrateegia	Key words: magnesium sulphate, preterm birth, cerebral palsy, neuroprotection. MESH: magnesium sulfate(teraupetic use); neuroprotective agents(therapeutic use); premature birth; Obstetric labor, Premature; cerebral palsy.
Tulemuste arv	SR: 5, RCT: 6 (MESH terminitega) Key words 11
Filtrid	Systematic Review , Randomised Controlled Trial .
Ajaline piirang	none
Muud piirangud	English language

Andmebaas	Cochrane Database of Systematic Reviews (CDSR),

	Database of Abstracts of Reviews of Effects (DARE)
Otsingustrateegia	Key words: magnesium sulphate (1), preterm birth(2), cerebral palsy(3), neuroprotection(4).
Tulemuste arv	(1)AND(2)AND(3)AND(4)-> 8 (1)AND(2)AND(3)-> 28 (1)AND(2)AND(4)-> 9
Filtrid	Systematic review
Ajaline piirand	none
Muud piirangud	English language

Andmebaas	Trip Database
Otsingustrateegia	Magnesium sulphate for fetal neuroprotection.
Tulemuste arv	8
Filtrid	Systematic review , Randomised controlled trial.
Ajaline piirand	none
Muud piirangud	English language

Andmebaas	Sum Search
Otsingustrateegia	Magnesium sulphate and cerebral palsy.
Tulemuste arv	26
Filtrid	Systematic review .
Ajaline piirand	none
Muud piirangud	English language

Andmebaas	Cochraine Central Register of Controlled Trials
Otsingustrateegia	Key words: magnesium sulphate, preterm birth, cerebral palsy.
Tulemuste arv	3
Filtrid	Randomised controlled trial.
Ajaline piirand	none
Muud piirangud	English language

Ohutuse tabel

MgSO4 kontsentratsioon (mmol/l)	Toime
0.8 – 1.0	Nomaalne plasma kontsentratsion.
1.7 – 3.5	Terapeutiline vahemik.
2.5 – 5.0	EKG muutused(P-Q intervalli pikenemine, QRS kompleksi laienemine).
4.0 – 5.0	Süvareflekside nõrgemine (patellaarrefleks, kannarefleks, biitsepsi- ja triitseptsirefleks).
> 5.0	Sõvaeflekside puudumine.
> 7.5	Sinoatriaal ja atrioventrikulaarne blokaad, respiratoornne paralüüs ja KNS depression.
> 12.0	Südameseikus.

Vererõhu monitooring	Hingamissageduse monitooring	Pulssi monitooring	Diureesi monitooring	Süvareflekisid e jälgimine	Plasma kontsentratsiioni jälgimine
2 tunni tagant	2 tunni tagant. Kui < 10, lõpeta MgSO4 infusiooni. Hingamisseiskuse korral manusta Ca glükonaat 1g 10 min jooksul.	2 tunni tagant	2 tunni tagant Kui <20 ml/t, lõpeta Mg SO4 infusiooni.	2 tunni tagant Kui reflekid puuduvad, lõpeta infusiooni.	Rutiinselt ei ole vaja määrata, kuna soovitatud doosiga toklilisus on vähetõenäoline.

Antidoot MgSO4 toksilisuse korral	Ca glükonaat 1 g (10 ml 10%) 10 min jooksul i/v

Tabelid võetud ravijuhendist: The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel. Antenatal magnesium sulphate prior to preterm birth for neuroprotection of the fetus, infant and child: national clinical practice guidelines. The University of Adelaide. 2010 Available from: www.nhmrc.gov.au. (8)