Review

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Antenatal magnesium sulfate for fetal neuroprotection: a critical appraisal and systematic review of clinical practice guidelines

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Abstract

Background: Magnesium sulfate is an accepted intervention for fetal neuroprotection. There are some perceived differences in the international recommendations on the use magnesium sulfate for fetal neuroprotection in preterm labor.

Content: This systematic review analyses the available clinical guidelines for the use of magnesium sulfate for fetal neuroprotection and compares the recommendations, and assesses the quality of guidelines. This provides the consensus, differences and explores the areas for future collaborative research. We searched databases of PUBMED, EMBASE, COCHRANE, Web of Science, LILACS; and included the national and the international clinical practice guidelines. We included seven guidelines out of 227 search results. We evaluated the methodological quality of guidelines using the Appraisal of Guidelines Research and Evaluation (AGREE II) tool and systematically extracted guideline characters, recommendation and supporting evidence base.

Summary: Five guidelines were of high quality and two were of moderate quality. One guideline achieved more than an 80% score in all the domains of AGREE II tool. All guidelines recommend use of magnesium sulfate for fetal neuroprotection. However, there are differences in other recommendations such as upper gestational age,

dose, duration, repeating treatment and use of additional tocolytics.

Outlook: Future guidelines should include recommendations on all aspects of magnesium sulfate therapy for fetal neuroprotection. Future research and international collaboration should focus on areas where there are no international consensual recommendations.

Keywords: guidelines; magnesium sulfate; neuroprotection; preterm birth.

Introduction

Preterm birth, spontaneous and iatrogenic, is associated with a significant risk of neonatal morbidity and mortality [1]. Although survival rates for preterm infants have increased, there is a substantial risk of medical complications and neurodevelopmental impairment [2]. The earlier the gestational age at birth, the higher is the risk. Intrauterine insults such as infection, inflammation, hypoxic ischemic encephalopathy and low birth weight are other risk factors associated with neurodevelopmental impairment [3–5]. The most frequently associated neurological outcomes are cerebral palsy and cognitive impairments [3]. The risk of cerebral palsy is increased by 30–80-fold in infants born before 30 weeks compared to term infants [4, 6, 7]. Other neurological morbidities include blindness, deafness, gross motor dysfunction, learning difficulties and developmental delay [6, 8, 9].

Several clinical studies and systematic reviews have evaluated the benefits and harm of antenatal administration of magnesium sulfate for fetal neuroprotection [5, 10–20]. However, there are still some controversies regarding the benefits, maternal and fetal side effects, appropriate dose and timing of administration, and the appropriate gestational age at which the intervention is beneficial [21, 22].

Guidelines are systematically developed statements based on the best available evidence [23]. Evidence based guidelines have been developed to assist healthcare

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providers achieve the best outcomes for their patients [24]. The development of effective guidelines requires the authors to follow standardized development methods and robust methodological quality [25]. The purpose of this systematic review is to critically appraise and systematically review the available national and international clinical practice guidelines for the antenatal use of magnesium sulfate therapy for fetal neuroprotection and compare the recommendations, evidence base, and assess the quality of guidelines. This in turn would allow identification of international consensus, differences and areas for future collaborative research.

Methods

Sources

A protocol with defined objectives, criteria for guideline selection and approaches to assessing outcomes was developed and registered with the PROSPERO (International Prospective Register of Systematic reviews) (Centre for Reviews and Dissemination; CRD42017071491, University of York, UK). This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [26, 27].

The initial literature search was performed by a clinical librarian (KN), and then independently by the first and second authors (PJ and MM) to compare the accuracy of search. Electronic databases of PUBMED, EMBASE, COCHRANE database, LILACS and Web of Science were searched for relevant guidelines using keywords of “preterm”, “magnesium sulfate” “fetal neuroprotection” and “guidelines”. In addition, guidelines websites such as the National Guideline Clearing House, the National Institute for Health and Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network, and obstetrics and gynecology associations or relevant professional societies such as the American College of Obstetrics and Gynecology, the Royal College of Obstetricians and Gynaecologists, the Society of Obstetricians and Gynaecologists of Canada, the American Academy of Family Physicians (AAFP), the Belgian Healthcare Knowledge Centre and the World Health Organization, were searched for additional guidelines.

Guideline selection

All titles and abstracts were screened by two authors (PJ and MM) independently to select the relevant guidelines

as per the defined selection criteria and a group consensus was achieved by the two primary authors (PJ and MM) for the included guidelines. The two primary reviewers then independently screened the full contents of all selected guidelines and rigorously assessed the eligibility based on the inclusion and exclusion criteria provided below. Any discrepancies between the reviewers were resolved by discussion.

Multidisciplinary clinical guidelines on the use of magnesium sulfate for the purpose of fetal neuroprotection were included with the following inclusion and exclusion criteria.

Inclusion criteria

1. Clinical practice guidelines of national or international bodies, published in the English language in the last 10 years. We included only the last 10 years to reflect the most recent evidence and up to date guidelines.
2. The recommendations on the use of magnesium sulfate therapy for fetal neuroprotection were documented.
3. Separate guidelines or as part of preterm birth guidelines were both included.

Exclusion criteria

1. Regional or institutional guidelines.
2. More than 10 years old.
3. Committee opinions, scientific impact papers, reviews and commentaries.
4. Guidelines that were not peer-reviewed or referenced.

Recommendations for clinical practice and supporting research evidence

Two independent reviewers (PJ and MM) extracted and mapped the pre-specified domains based on the descriptive analysis.

Descriptive analysis was undertaken to describe the general characteristics and recommendations in each guideline. Selected guidelines were reviewed for general descriptions such as year of publication, updates if they were part of preterm guidelines or separate guidelines, number of recommendations, level of evidence for recommendations and grading of recommendations [28].

The following pre-specified recommendation domains included: use of magnesium sulfate for fetal

neuroprotection recommended, an upper gestational age for the use of magnesium sulfate, recommended dose and duration, use of magnesium sulfate irrespective of cause of preterm labor and plurality, repeat dose recommended if the patient had not given birth in 24 h, recommended to discontinue other tocolytics with magnesium sulfate and recommended to monitor adverse effects. A recently published systematic review of guidelines on preterm birth includes international, national and regional guidelines and reviews all general aspects of preterm birth [29]. With regards to use of magnesium sulfate, this previously published review addresses only one question: “if magnesium sulfate is recommended or not in preterm labor for fetal neuroprotection”. This current systematic review is focused on in depth assessment of national and international guidelines with specific focus on use of magnesium sulfate for fetal neuroprotection, which is a significant and topical issue. We have reviewed nine recommendations in each included guidelines.

Quality assessment

The Appraisal of Guidelines Research and Evaluation (AGREE II) tool was used for assessing the methodological quality of each guideline [30, 31]. The appraisal was performed on the online AGREE II guideline appraisal tool (<http://www.agreetrust.org/appraisal>). Each of the 23 items in the six domains of the AGREE II tool is assessed on a seven-point scale response based on key methodological principles. A score of 1 indicates an absence of information or that the concept is very poorly reported. A score of 7 means that the quality of reporting is exceptional, and all of the criteria and considerations articulated in the user’s manual were met. A score between 2 and 6 indicates that the reporting of the AGREE II item does not fully comply with criteria or considerations. The percentage of maximum score in each domain was calculated. The guidelines were assessed and scored by two authors (PJ and MM), and any discrepancies resolved by consensus and discussion with the senior author (SL).

Analysis

A guideline score was calculated by the summation of the pre-specified domains and standardized using a pre-scribed equation [30]. Guidelines were categorized into low quality (0–33%), moderate quality (34–66%) and high quality (67–100%).

Results

Literature search and guidelines selection

The literature search in electronic databases and websites of relevant professional bodies yielded 227 results. After screening, titles and abstracts against inclusion and exclusion criteria and removal of duplicates nine full papers were reviewed. Two were excluded as they were a committee opinion or did not include recommendations for magnesium sulfate for fetal neuroprotection [32, 33]. Seven guidelines were incorporated for systematic review. These are

1. Australian and New Zealand National clinical practice guidelines, Antenatal Magnesium Sulfate for Neuroprotection of Fetus, Infant and Child (ANZ) [34]
2. Society of Obstetricians and Gynaecologists of Canada clinical practice guidelines on Magnesium Sulfate for Fetal Neuroprotection (SOGC) [35]
3. Clinical practice guidelines from Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland — Antenatal Magnesium Sulfate for Fetal Neuroprotection (RCPI) [36]
4. Prevention of Preterm Birth in Women at Risk: Selected Topic, Belgian Healthcare Knowledge Centre (KCE) [37]
5. World Health Organization — WHO recommendations on interventions to improve preterm birth outcomes (WHO) [38]
6. National Institute of Health and Care Excellence — Preterm Labour and Birth (NICE) [39]
7. French College of Obstetricians and Gynaecologist — Prevention of Spontaneous Preterm Birth: Guidelines for Clinical Practice (CNGOF) [40]

Figure 1 shows the PRISMA flow diagram of the literature search.

General characteristics of guidelines

Three (ANZ, SOGC, RCPI) of the seven guidelines were separate guidelines specifically addressing the topic of magnesium sulfate use for fetal neuroprotection. In the remaining four guidelines, the topic of magnesium sulfate for fetal neuroprotection was included in the general guidelines of prevention and management of preterm labor. Year of publication ranged from 2010 to 2017. The RCPI guidelines were the only ones that were updated (2013). All the included guidelines were from the

Figure 1: PRISMA flow diagram.

Guidelines on use of magnesium sulfate for fetal neuroprotection.

Table 1: General characteristics of guidelines.

	ANZ	SOGC	RCPI	KCE	WHO	NICE	CNGOF
Status							
Part of preterm guidelines				✓	✓	✓	✓
Separate guidelines	✓	✓	✓				
Year of publication	2010	2011	2013	2014	2015	2015	2017
New	✓	✓	✓	✓	✓	✓	✓
Updated			✓				
Organizational							
Professional body	✓	✓	✓	✓	✓	✓	✓
Governmental							
Recommendations							
Number of recommendations	7	11	7	1	1	5	2
Evidence level stated	No	Yes	No	Yes	Yes	No	Yes
Recommendation GRADE stated	Yes	Yes	No	Yes	Yes	Yes	Yes

professional bodies. Details of guidelines characteristics are presented in Table 1.

Recommendations for clinical use

All of the seven reviewed guidelines recommend the use of the magnesium sulfate for fetal neuroprotection in premature labor. The recommendation to use magnesium sulfate was the first recommendation in all the guidelines. The evidence level was 1 and recommendation

GRADE was level A, in three guidelines (SOGC, ANC, CNGOF), moderate evidence level and a strong recommendation was reported by the WHO and high level of evidence and strong recommendation was given by the KCE. Other guidelines did not report the evidence level and GRADE for recommendations. The number of recommendation statements varied from 1 to 11. Two guidelines with one recommendation statement did include the recommendation for using magnesium sulfate, upper gestational age and duration of use. In six guidelines the upper gestational age for the use of magnesium sulfate

was 32 weeks, whereas the NICE guidelines recommends to offer up to 29 weeks + 6 days and to consider using up to 33 weeks + 6 days.

Four guidelines (SOGC, ANZ, RCPI, NICE) recommend a dosage of 4 g loading dose followed by 1 g/h maintenance dose for 24 h or until birth. The Belgian guidelines recommend use for not more than 24 h but do not recommend a dose. The French guidelines recommend using for 12 h or until birth, while the WHO guidelines do not suggest the dose and timing. Three guidelines (SOGC, ANZ, CNGOF) recommend using irrespective of the cause of preterm labor and another three do not make any recommendation regarding the cause of preterm labor. Three guidelines recommended use of magnesium sulfate irrespective of plurality (ANZ, WHO, CNGOF) and the remaining three did not have any recommendation. Repeating the dose in 24 h was recommended in two guidelines (ANZ and RCPI), while the SOGC suggested there was insufficient evidence to make recommendations and it was not stated in the remaining four guidelines. A recommendation to discontinue other tocolytics with magnesium sulfate was given in the SOGC guidelines and the ANZ guidelines recommends only stopping if there was hypotension, others did not make any recommendations. Four guidelines recommended to monitor adverse effects (ANZ, SOGC, RCPI, NICE) and another two (WHO KCE, and CNGOF) did not make any recommendation (see Table 2).

AGREE II scoring

The AGREE II scoring for each guideline is presented in Table 3. Five guidelines were of overall high quality and two were of moderate quality as per AGREE II collaboration. The scores for each domain varied between the guidelines. The scores in different domains varied from 80% to 98% in ANZ guidelines; from 64% to 92% in SOGC; from 21% to 93% in RCPI; from 86% to 100% in KCE; from 74% to 90% in WHO; from 64% to 100% for NICE; from 29% to 80% in CNGOF. The Belgian KCE achieved more than 80% of maximum score in all the domains, and ANZ, NICE and WHO guidelines did so in five of six domains. Highest scores were achieved in the domain of “scope and purpose” where lowest scores were achieved in the domain of “editorial independence”. Editorial independence addresses if the views of the funding body or the competing interests of the members of the committee has any effect on the publication. Low scores mean that they were not recorded, and therefore difficult to ascertain if there was any influence.

Table 2: Guideline recommendations.

Recommendations	ANZ	SOGC	RCPI	KCE	WHO	NICE	CNGOF
Use of magnesium sulfate for fetal neuroprotection recommended	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Upper gestational age for use	30	31+6	32	32	32	33+6	32
Recommended dose	4 g loading, 1 g/h maintenance 24 h or until birth	4 g loading, 1 g/h maintenance 24 h or until birth	4 g loading, 1 g/h maintenance 24 h or until birth	4 g loading, 1 g/h maintenance 24 h or until birth	Insufficient evidence to recommend	4 g loading, 1 g/h maintenance 24 h or until birth	4 g loading, 1 g/h maintenance 12 h or until birth
Recommended duration	Yes	Yes	*	No more than 24 h	*	*	Yes
Use recommended irrespective of cause of preterm labour	Yes	*	*	*	Yes	*	Yes
Use recommended irrespective of plurality	Yes	Insufficient evidence to recommend	Yes	*	*	*	*
Repeat dose recommended if not given birth in 24 h	Yes	Yes	*	*	*	*	*
Recommended to discontinue other tocolytics with magnesium sulfate	Stop if hypotension	Yes	*	*	*	*	*
Recommended to monitor adverse effects	Yes	Yes	Yes	*	*	Yes	*

*No recommendation.

Table 3: AGREE-II scores.

AGREE-II domains	ANZ	SOGC	RCPI	KCE	WHO	NICE	CNGOF
Scope and purpose	98%	95%	93%	100%	90%	100%	69%
Stakeholder involvement	98%	83%	53%	95%	74%	83%	52%
Rigor of development	90%	82%	45%	98%	91%	95%	60%
Clarity of presentation	90%	92%	90%	86%	95%	88%	80%
Applicability	80%	86%	45%	96%	91%	82%	27%
Editorial independence	96%	64%	21%	86%	92%	64%	57%
Overall quality	High	High	Moderate	High	High	High	Moderate

Discussion

All the seven guidelines strongly recommend the use of magnesium sulfate for fetal neuroprotection for preterm fetus, with a high level of the evidence base. Most recommend using up to 32 weeks at a dose of 4 g loading doses and 1 g/h of maintenance, similar to management of severe pre-eclampsia. This is not surprising as the scientific evidence used for making these recommendations is all based on the same available research evidence. This type of international consensus is particularly beneficial when practitioners or patients are moving from country to country, which is not uncommon.

Three of the seven were separate guidelines on the use of magnesium sulfate for fetal neuroprotection and in the remaining four the topic was included in the general guidelines on preterm birth. More substantial guidelines, for example, the NICE guidelines which has 247 pages, can sometimes make it difficult to find the required recommendations for busy clinicians. The rigor of development and clarity of presentation was proper in all the guidelines, but the applicability did not score well.

Although there is good evidence of the benefits and the use of magnesium sulfate is recommended in many international guidelines, there are many units which have yet to implement these recommendations [41, 42]. The challenges for implementation may be multifactorial, including the availability of resources [43]. There is also a lack of consensus on repeating dosage, use in multiple pregnancies and concomitant use with other tocolytics, which in turn reflects a lack of adequate evidence base. A recent meta-analysis of individual patient data showed that there was no significant difference in the treatment effect of antenatal magnesium sulfate based on gestational age, cause of preterm birth, the total dose given and whether a maintenance dose was used. Benefits were noted regardless of these variations [44]. However, individual organization level guidelines

and protocols should include these recommendations to assist clinicians based on the best available evidence, as applicable locally [45].

Recommendations from guidelines reflect available evidence and therefore are likely to be similar when that evidence is available to all. There may not be a valid recommendation that can be made, or the recommendations may vary based on opinions if there is no substantial or agreed evidence base. These areas, where clinically important, should become the focus of future research and international collaboration. Given the importance that effective neuroprotection can offer to the preterm fetus with long term minimization of disability the areas of uncertainty outlined above should be addressed without delay.

Conclusion

All the reviewed international guidelines uniformly recommend the use of magnesium sulfate for fetal neuroprotection in preterm birth. There are some differences in recommendations on an upper limit of gestational age to use, repeating dosage if delivery does not occur, and concomitant use of tocolytics and duration of use.

Future research and international collaboration should focus on areas where there is not sufficient evidence to make international consensual recommendations. Future guidelines should include recommendations on all aspects of magnesium sulfate therapy for fetal neuroprotection and individual organizations should develop their guidelines incorporating local applicability and continue to audit the outcomes.

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Author contributions: PJ conceived the idea; PJ, MM and SL were involved in design of the research protocol.

PJ and MM were involved in literature search with the help of a clinical librarian. PJ and MM undertook screening of search results, full paper retrieval and study selection. PJ and IF extracted the data. PJ and MM were involved in quality assessment using the AGREE II tool. SL contributed in preparing initial draft. All authors contributed to the drafts and final version of the manuscript, tables and figures.

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