Journal of Neonatal Biology
ISSN: 2167-0897

Willhelm et al., J Neonatal Biol 2012, 1:2
DOI: 10.4172/2167-0897.1000106

Research Article Open Access

Systematic Cochrane Reviews in Neonatology: A Critical Appraisal

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Abstract

Background: There is a lack of up-to-date, systematic reviews that critically assess the role and potential limitations of Evidence based medicine (EBM) and systematic reviews in neonatology.

Methods: We performed a systematic literature review of all Cochrane Reviews published between 1996 and 2010 by the Cochrane Neonatal Review Group (CNRG). Main outcome parameter: Assessment of the percentage of reviews that concluded that a certain intervention provides a benefit, percentage of reviews that concluded that no benefit was seen, and percentage of studies that concluded that the current level of evidence is inconclusive.

Results: In total, 262 reviews were enrolled, most of which included exclusively preterm infants (146/262). The majority of reviews assessed pharmacological interventions (145/262); other important fields included nutritional (46/262), and ventilatory issues (27/262). In 42/262 reviews a clear recommendation in favor of a certain interventions was given, while 98/262 reviews concluded that certain interventions should not be performed. However, the largest proportion of reviews was inconclusive (122/262), and did not issue specific recommendations. The proportion of inconclusive reviews increased from 30% (1996-2000), to 50% (2001-2005), and finally to 58% for the years 2006-2010. Common reasons for inconclusive reviews were small number of patients (105), insufficient data (94), insufficient methodological quality (87), and heterogeneity of studies (69).

Conclusions: There is an ongoing need for high quality research in order to reduce the proportion of inconclusive meta-analyses in the field of neonatology. Funding and research agencies will play a vital role in selecting the most appropriate research programs.

Keywords: Evidence based medicine; Cochrane reviews; Neonatology

Introduction

Undoubtedly, evidence-based medicine has contributed substantially to improving the quality of medicine in general, and in neonatology in particular [1]. The Cochrane Neonatal Review Group (CNRG) is one of 50 Review Groups within the Cochrane Collaboration, and it is one of the most active ones [2]. There are a number of examples that illustrates the importance of systematic reviews in improving the delivery of medical care, for example, administration of antenatal steroids, surfactant replacement therapy, hypothermia for hypoxic ischemic encephalopathy, and probiotics to prevent necrotizing enterocolitis.

A systematic review published in 1990 demonstrated that antenatal administration of corticosteroids substantively reduced both neonatal mortality and morbidity without negatively impacting on maternal outcomes [3]. After recommendations were issued by a number of national societies that corticosteroids should be given to all women with impending preterm birth [4], a dramatic change in practice with a more than 3-fold increase in antenatal corticosteroid exposure in very low birth weight infants in the Vermont Oxford Neonatal Network was seen [5]. Some authors argue that if a system for cumulative research synthesis had been in place, antenatal corticosteroids may have been adopted as a standard of care much earlier [6,7]. Moreover, and of importance, Cochrane reviews have also contributed to identifying interventions that are ineffective or harmful, for example, administration of antenatal thyrotrophin-releasing hormone and early postnatal administration of dexamethasone [7,8].

However, although these examples undoubtedly illustrate the potential importance and impact of the Cochrane database in the field of neonatology, no formal, up-to-date analysis of all published systematic Cochrane reviews has been performed with regard to the number of reviews with a definitive conclusion in favor of a certain intervention, number of reviews with a definitive conclusion against a certain intervention, and number of inconclusive reviews.

Methods and Clinical Questions

We conducted a systematic literature review including all reviews from the Cochrane Neonatal Review Group (CNRG) (http://neonatal.cochrane.org) from 1996 until 2010 (total number: 267). Reviews that specifically addressed maternal/parental issues were excluded from the study (number=5).

The following data were retrieved from the CNRG database: 1) Origin of publication by country; 2) Gestational age of included study populations; 3) Number of included RCTs and number of patients; 4) Time of publication; 5) Type of intervention (pharmacological, non-pharmacological, etc.).

The main outcome parameter was

a) Number (percentage) of reviews with a definitive conclusion

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Received April 06, 2012; **Accepted** July 23, 2012; **Published** July 26, 2012

Citation: Willhelm C, Girisch W, Gottschling S, Gräber S, Meyer S (2012) Systematic Cochrane Reviews in Neonatology: A Critical Appraisal. J Neonatal Biol 1:106. doi:10.4172/2167-0897.1000106

in favor of a certain intervention; b) Number (percentage) of reviews with a definitive conclusion against a certain intervention; c) Number (percentage) of inconclusive reviews.

We subsequently analysed the specific reasons why reviews were considered inconclusive as provided by the authors. We also evaluated whether differences with regard to the primary outcome parameters were seen between 3 different, a priori defined time episodes (1996-2000; 2001-2005; 2006-2010); (also we assessed potential differences with regard to the primary outcome parameters between initial publications and the latest up-dates of reviews).

All data were retrieved from the CNRG and stored in an electronic database, using SPSS 18.0 (SPSS, Chicago, IL, USA). If necessary, the original publications were retrieved from the Cochrane database and hand-searched for missing data with regard to our study questions. Information was added to the database if indicated. Data are presented as mean, median, standard deviation and range.

Results

In total, 262 reviews were included in this study; five reviews were excluded because they dealt exclusively with maternal or parental issues. As depicted in figure 1, the vast majority of Cochrane reviews were performed in Western, industrialised countries (Australia, North America, and Europe: 247/262), while only a minority of papers originated from developing countries (15/262). The USA and Canada both contributed 44 reviews, while the United Kingdom was the major contributing country within Europe (35/262). Most studies were performed exclusively in preterm neonates (146/262), 42/262 included both pre- infants and term infants. 13 reviews involved term neonates only; in 35 reports no specific data with regard to gestational age was provided (more detailed information with regard to gestational age and birth weight is given in figure 2a and 2b. In 26 Cochrane reviews, no RCTs were available for enrolment.

The mean number of studies initially considered for a specific review was 12.6 (median: 7; range: 0-111), while the number of

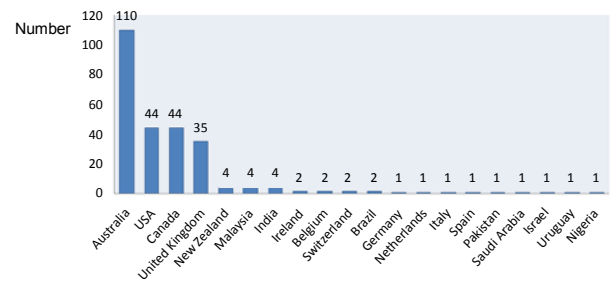

Figure 1: Country of origin.

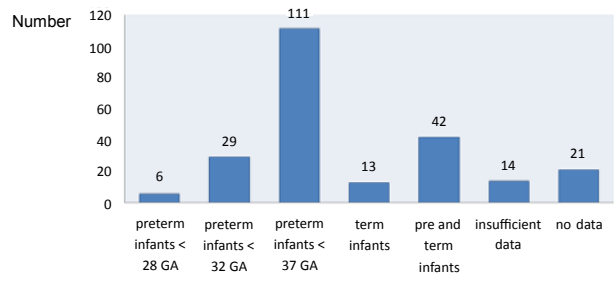

Figure 2a: Gestational age of neonates of included studies.

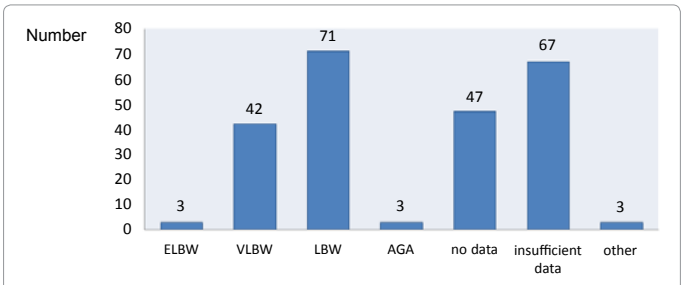

Figure 2b: Birth weight of neonates of included studies.

	1996-2000	2001-2005	2006-2010
Mean	7.0	4.9	4.4
SEM	0.7	0.8	0.8
Minimum	0	0	0
Maximum	44	64	28

Table 1a: Number of studies included according to time period of publication.

	1996-2000	2001-2005	2006-2010
Mean	930.9	697.9	483.7
SEM	139.6	217.2	90.8
Minimum	0	0	0
Maximum	546	21,070	2,701

SEM: Standard error of the mean

Table 1b: Number of patients included according to time period of publication.

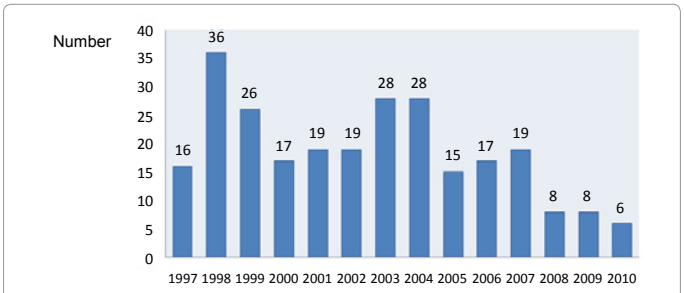

Figure 3: Year of publication.

studies finally included was 5.5 (median: 3; range: 0-64), the number of patients included was 727.9 (median: 208; range: 0-21,070). Table 1a and 1b provide specific information with regard to the number of included trials and patients per review and date of publication.

As shown in figure 3, initially a rather even distribution over time of published reviews was seen; however, recently, a lower number of systematic reviews have been published (2006-2010). This trend is also illustrated when grouped into 3 cohorts (1996-2000: 95; 2001-2005: 109; 2006-2010: 58). In total, 167/262 of reviews have been up-dated since their original publication while the remaining 95 papers have not been revised (1996-2000: 86 up-dated; 2001-2005: 68 up-dated; 2006-2010: 13 up-dated).

When looking at type of intervention, the majority of reviews examined pharmacological interventions (145/262), and nutrition (46/262), and ventilation and ventilatory support (27/262), while the remaining reviews analysed a variety of issues including surgery/invasive procedures, non-pharmacological pain therapy, physiotherapy, neuro developmental issues, and others (Figure 4).

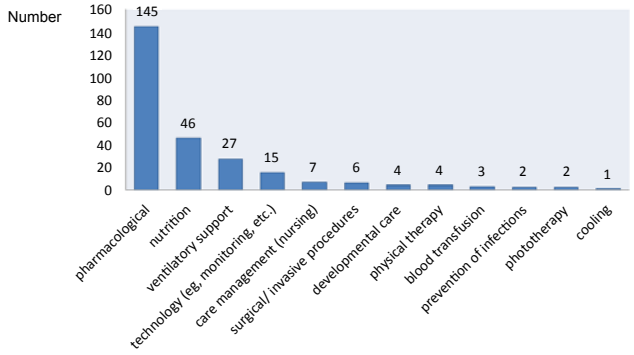

Figure 4: Types of interventions assessed by Cochrane reviews.

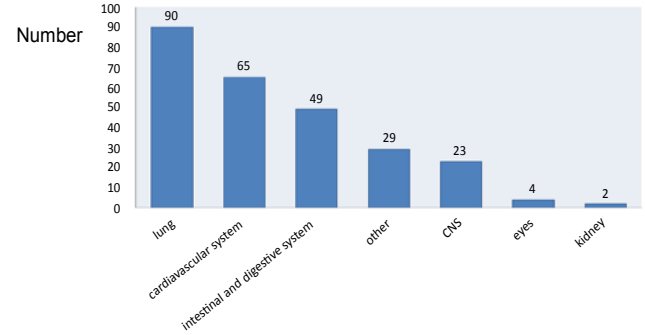

Figure 5: Number of reviews/therapeutic interventions with regard to organ system.

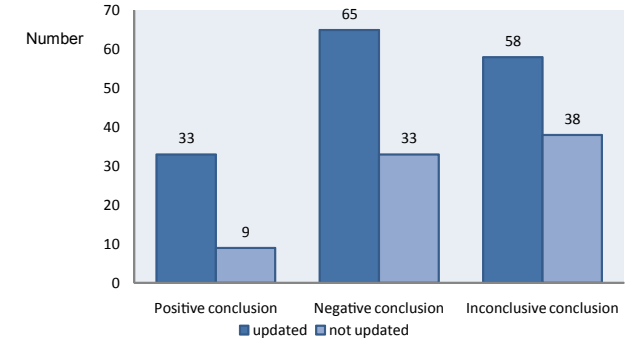

Figure 6: Number of conclusive and inconclusive reviews depending on status up-dated or not up-dated.

With regard to organ system, the following organs were analysed: lung (90/262), cardiovascular system (65/262), intestinal and digestive system (49/262), central nervous system and eyes (23+4/262), kidney (2/262), and others (49/262) (Figure 5).

Of all 262 reviews, 42 of reviews gave a clear recommendation in favor of a certain interventions (positive recommendation), while 98/262 reviews concluded that certain interventions should not be performed (negative recommendation). However, the largest proportion of reviews was inconclusive (122/262), and did not provide specific recommendations. Seven out of those 122 reviews issued partial or conditional recommendations that cannot be generalised for neonates or preterm infants. Of note, the percentage of inconclusive reviews increased from 30% (1996-2000), to 50% (2001-2005), and finally to 58% for the years 2006-2010. There were 33 updated reviews with a positive recommendation and 65 with a negative recommendation, while 69 reviews were inconclusive. In non-updated reviews, 9 issued a positive, 33 a negative recommendation, and 53 were inconclusive (Figure 6). The number of reviews with conclusions changed/not changed depending on status updated/not up-dated are provided in figure 7.

The 3 most common reasons (multiple entries possible) for inconclusive reviews were small number of patients (105), insufficient data (94), poor and insufficient methodological quality (87) (Figure 8).

Discussion

Evidence based medicine (EBM) plays an ever more important role in the delivery of medicine in our days, including in the field of neonatology. Recent reports have shown good agreement between Cochrane reviews and local neonatal guidelines at the level of university hospitals [9], although discrepancies between recommendations from systematic reviews and local practice continue to exist.

In this review, we demonstrated that the use of systematic reviews as provided by the CNRG plays an important role in providing disseminating the best available evidence, thus contributing to the provision of good medical care at the bedside. A substantial proportion of systematic reviews provided data with regard to the question whether a certain intervention should or should not be performed (42 positive; 98 negative). This will provide the physician at the bedside with invaluable information with regard to both optimal and unnecessary treatment modalities. However, interpretation and possibly implementation of these data should only be done in conjunction with "local modifiers", for example the decision to use intramuscular vitamin A to prevent Bronchopulmonary Dysplasia (BPD) may depend on "local" BPD incidence rates. It is also noteworthy that the vast majority of reviews published in the CNRG originate

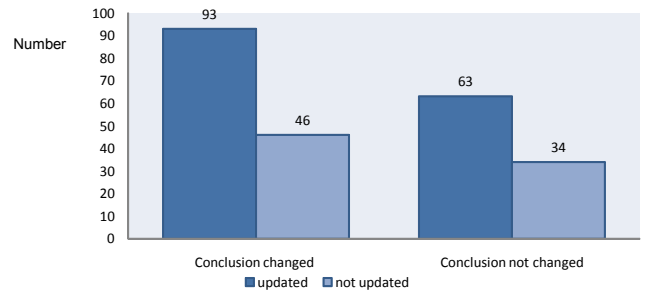

Figure 7: Number of reviews with conclusions changed/not changed depending on status updated/not up-dated (*).

(*) Only 236 reviews were included since 26 reviews did not include data.

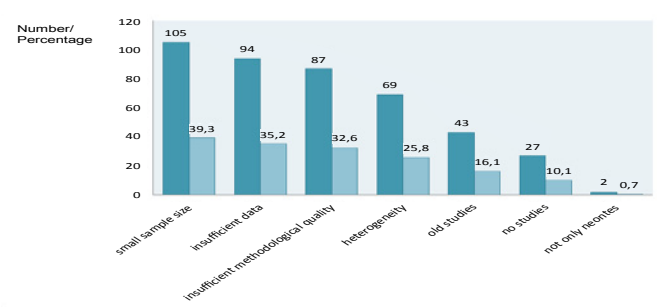

Figure 8: Main reasons for inclusive data in Cochrane reviews.

from Western, industrialised countries. Thus, the recommendations issued in these reviews are almost exclusively applicable to the field of neonatology as practised in industrialised countries, and will exclude the majority of neonates being born and cared for in the developing world. However, recently efforts (through initiatives such as the Effective Health Care Alliance and the "Sea-orchid" consortium), have been undertaken to disseminate knowledge from the CNRG to low- and middle-income countries to ensure that care practices are evidence based and scarce resources will be used and allocated appropriately [7,10].

However, and of note, our study also demonstrated that a substantial percentage of systematic Cochrane reviews was inconclusive, and did not provide any recommendation with regard to a specific intervention. This is in line with previous reports on this subject [11,12]. These reviews usually conclude that, following an extensive literature search and appraisal, "insufficient trial evidence was found to guide clinical practice". Often only a trend can be seen, or statistically significant changes can only be seen for short-term outcome parameters (e.g. Ventilated days) [13], but not for long-term outcome parameters (e.g. the incidence of death or chronic lung disease at 36 weeks, intraventricular haemorrhage grade 3 or 4 or periventricular leucomalacia) [14]. Moreover, it is noteworthy that a recent analysis demonstrated that many apparently conclusive Cochrane neonatal meta-analyses may become inconclusive when the statistical analyses take into account the risk of random error due to repetitive testing [15]. The most common reasons for inconclusive data in Cochrane reviews are depicted in figure 6. Moreover, in previous reports, neonatal Cochrane meta-analyses have been criticised for a lack of a priori plan for heterogeneity assessment and how to handle heterogeneity in case it exists [16].

The most common reasons for failure to generate specific recommendation in our analysis were usually attributed to small number of patients, poor and insufficient methodology, and heterogeneous study populations. Although defining clinical uncertainty and thereby generating new research questions is a fundamental driving force for evidence based medicine, clinicians at the bedside will find this frustrating and unhelpful [7]. However, by identifying important gaps in the evidence Cochrane reviews have the potential to promote high-quality RCTs in the field of perinatology (eg, Collaborative quality improvement initiatives such as the WOMBAT collaboration in Australasia (http://www.wombatcollaboration.net/)) [7]. This can be illustrated by the fact that several recent large RCTs trials in perinatal medicine have been undertaken when Cochrane reviews had highlighted important areas of clinical uncertainty. Examples relevant to pregnancy and childbirth management strategies have been well described. [7,17]; recent examples of neonatal interventions include a) The "Benefits of Oxygen Saturation Targeting" (BOOST) and "Pulse Oximetry Saturation Trial for Prevention of Retinopathy of Prematurity" (POST ROP), [18], and the "Caffeine for Apnoea of Prematurity" (CAP) trial [19]. Moreover, clinical researchers have conceptualised a research cycle that includes systematic review and observations of the effects in practice [20]. Of note, so far Australia has been by far the largest contributor to the CNRG.

However, if the above outlined approach is bound to be successful, one would expect an increasing number of high quality (and likely conclusive) reviews that are based on sophisticated research data. However, on the contrary, and somewhat surprising, we noted a tendency with an increase in the number of inconclusive reviews over the 15-year study period, thus generating more uncertainty than certainty in the field of neonatology. This is in line with a previous study on this subject [12], and is likely attributed to the fact that the number of RCTs and number of patients per Cochrane review decreased over the three, a priori defined study episodes (Table 1a and 1b). Moreover, when specifically comparing up-dated vs. non-up-dated reviews, the number of conclusive (either positive or negative recommendation) reviews was substantially higher in up-dated reviews (98/167 vs. 42/95), and the number of up-dated reviews was substantially higher in the early periods. The decrease in the number of up-dated reviews in the CNRG is in part attributable to the time-consuming process of frequent up-dating as mandated by the Cochrane protocol [7,21]. Therefore, new strategies were developed by the CNRG to prioritize reviews for updating based on perceived clinical importance and knowledge of availability of new evidence [7,21].

Moreover, our results may also suggest an alternative scientific research approach in neonates which may complement the conventional paradigm of research [22]. Being born as a very premature infant constitutes a medical emergency with numerous medical problems, possibly occurring simultaneously (surfactant deficiency, patent ductus arteriosus, metabolic dysfunction, intraventricular haemorrhage, etc.). Therefore, it is quite unlikely for a single intervention (e.g. use of diuretics or permissive hypercapnea to prevent chronic lung disease) to impact significantly on crude outcome parameters. Deducing that these interventions have no place in neonatology could possibly be short-sighted as they may very well have shown a positive trend.

We suggest that future, clinical studies in neonatology should also assess a "compound" interventional approach, e.g. a lung protective approach (e.g. permissive hypercapnea plus use of diuretics, plus fluid restriction) vs. a conventional approach. These studies should combine two or more interventions that have proved to be partially beneficial (positive trend) and assess prospectively whether the combination of these interventions will improve outcome parameters in the premature infant. This change in paradigm will have the potential to contribute more substantially to our knowledge in the complex field of neonatology and impact more profoundly on our therapeutic approach than studies that assess single interventions alone. In line with this "new" strategy, a recent study has demonstrated that implementation of a number of potentially better practices (i.e., (1) exclusive use of bubble continuous positive airway pressure (bCPAP), (2) provision of bCPAP in the delivery room, (3) strict intubation criteria, (4) strict extubation criteria, and (5) prolonged CPAP to avoid supplemental oxygen) reduced the need for mechanical ventilation, surfactant, and supplemental oxygen as well as reduced hypotension among infants born before 33 weeks' gestation without adverse consequences. Moreover, in this report the costs for equipment and surfactant were lower [23].

However, multi-interventional protocols may have obvious drawbacks as well-namely, it is difficult to know what is helping or hurting when several parameters are manipulated simultaneously-as a matter of fact it is this difficulty why RCTs were designed in the first place. Thus, we should be prudent and see whether new statistical methods - made possible by bigger and better computers that allow analysis of much bigger datasets will allow meaningful results to be derived from more complex study designs.

In addition, given the limited financial and human resources that are nowadays available in the medical arena, future emphasis must be on long-term outcomes that are vital to infants, their families as well as to health care workers. Importantly, in the future the effects of interventions not only on survival, but on long-term morbidity must be considered as well [7,18]. This change in paradigm is

particularly important in perinatal medicine as there is a potential for interventions to improve short term outcomes but also to increase the likelihood of adverse longer term outcomes in surviving neonates (eg, administration of systemic corticosteroids in the first few days of postnatal life improves short term respiratory function, but also increases the rate of adverse neurological effects).

Conclusions

In summary, this is the first systematic analysis of the potential role and limitations of Cochrane reviews in the field of neonatology. Our findings demonstrate that there is a need for more high quality research in the field of neonatology. The realization of high quality research will in turn result in more systematic reviews that will come to a clear conclusion (i.e. in favor or against a certain intervention, or treatment modality, etc.), as demonstrated in the up-dated versions of Cochrane reviews. It will be of paramount importance that funding and research agencies will support those research programmes that address the most relevant issues in the field of neonatology. While our study focussed on practical issues, there is no question that the CNRG and Cochrane reviews play an outstanding role in providing systematic, up-to-date research data and importantly, generating and prioritizing new research questions for funding, action, and clinical collaboration-thus informing both practice and research audiences [17,24-26]. Moreover, although Cochrane reviews are not a substitute for guidelines issued by national or international medical societies, the CNRG has acted as a driving force and promoter of implementing guidelines on a international and national level (eg: www.awmf.org/leitlinien/detail/ll/024-014.html).

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