

# Ability of a meta-analysis to prevent redundant research: systematic review of studies on pain from propofol injection

Céline Habre,<sup>1</sup> Martin R Tramèr,<sup>2,3</sup> Daniel M Pöpping,<sup>4</sup> Nadia Elia<sup>2,5</sup>

<sup>1</sup>Department of Radiology, Geneva University Hospitals, 4 rue Gabrielle-Perret-Gentil, CH-1211 Geneva 14, Switzerland

<sup>2</sup>Division of Anaesthesiology, Geneva University Hospitals, Geneva, Switzerland

<sup>3</sup>Faculty of Medicine, University of Geneva, Geneva, Switzerland

<sup>4</sup>Department of Anaesthesiology and Intensive Care, University Hospital Münster, Münster, Germany

<sup>5</sup>Institute of Global Health, Faculty of Medicine, University of Geneva, Geneva, Switzerland

Correspondence to: C Habre  
celine.habre@hcuge.ch

Cite this as: *BMJ* 2014;**349**:g5219  
doi: 10.1136/bmj.g5219

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;**349**:g5219

## thebmj.com

Prevention of pain on injection of propofol: systematic review and meta-analysis (*BMJ* 2011;**342**:d1110)

## STUDY QUESTION

What has been the impact of a systematic review with meta-analysis, published in 2000 and summarising the evidence on the prevention of pain from propofol injection, on the design of subsequently published trials?

## SUMMARY ANSWER

Although some methodological problems highlighted by the research agenda of the systematic review have been dealt with, the overall impact of the review on the design and clinical relevance of subsequent research has remained insufficient, resulting in the publication of a large number of irrelevant and thus unethical trials.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Systematic reviews may guide researchers in assessing the need for further investigations, thus avoiding unnecessary research. The present analysis calls for the development of strategies to improve dissemination of research agendas of systematic reviews and a greater incitement to use systematic reviews to inform rational trial designs.

## Selection criteria for studies

We compared the 56 “old” trials that had been included in the published systematic review with all “new” trials, published from January 2002 to January 2013, and identified using the same search strategy.

## Primary outcomes

The systematic review had identified the most efficacious treatment to prevent the pain from propofol injection (number needed to treat 1.8) and had highlighted the need for more paediatric trials and improved blinding. We set out to check whether these deficiencies had been tackled in subsequent trials. We also checked whether the most effi-

acious treatment was used as a comparator and whether the design of new trials that cited the review differed from those not citing it. Finally, we evaluated the proportion of clinically relevant new trials—that is, trials that compared an experimental intervention with the most efficacious treatment, or that were conducted in children.

## Main results and role of chance

136 new trials were retrieved. Compared with the 56 old trials, new trials were published more often (median number of trials/year 12 (range 7–20) v 2.5 (0–9),  $P < 0.001$ ), with no obvious decreasing trend. New trials were more often optimally blinded, used the most efficacious treatment more often as a comparator, and showed a tendency towards a greater proportion of paediatric trials. However, all these improvements remained marginal. Although 72.8% ( $n=99$ ) of new trials cited the systematic review, their designs were similar to those not citing it. Only 36.0% ( $n=49$ ) of new trials were considered clinically relevant.

## Bias, confounding, and other reasons for caution

Our analysis has methodological limitations. We did not consider trials that were published between January 2000 and December 2001. Some authors of new trials may have remained unaware of the systematic review even though we selected trials that were published after 2002. We did not contact authors to ask for reasons underlying the choice of their study design. Improvements in blinding may reflect the general improvement in the reporting of randomised trials owing to the implementation of the CONSORT recommendations.

## Study funding/potential competing interests

MRT is also a coauthor of the analysed systematic review. This study did not receive specific funding.

Comparison of trials published before (old) and after (new) systematic review

Characteristics	New v old trials	Difference in % (95% CI)
No of trials (No of participants)	136 (19 778) v 56 (6 264)	
Optimal blinding (%)	38.2 v 10.7	27.5 (16.0 to 39.0)
Paediatric trials (%)	12.5 v 5.4	7.1 (–1.0 to 15.2)
Trial designs including most efficacious intervention (%)	27.9 v 12.5	15.4 (4.0 to 26.9)

# Effect of implementation of Integrated Management of Neonatal and Childhood Illness programme on treatment seeking practices for morbidities in infants: cluster randomised trial

Sarmila Mazumder,<sup>1</sup> Sunita Taneja,<sup>1</sup> Rajiv Bahl,<sup>2</sup> Pavitra Mohan,<sup>3</sup> Tor A Strand,<sup>4</sup> Halvor Sommerfelt,<sup>5</sup> Betty R Kirkwood,<sup>6</sup> Nidhi Goyal,<sup>1</sup> Henri Van Den Hombergh,<sup>3</sup> Jose Martinez,<sup>5</sup> Nita Bhandari,<sup>1</sup> on behalf of the Integrated Management of Neonatal and Childhood Illness Evaluation Study Group

<sup>1</sup>Centre for Health Research and Development, Society for Applied Studies, New Delhi 110016, India

<sup>2</sup>Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva, Switzerland

<sup>3</sup>UNICEF India Country Office, New Delhi, India

<sup>4</sup>Centre for International Health, University of Bergen, Norway

<sup>5</sup>Centre for Intervention Science in Maternal and Child Health, Centre for International Health, University of Bergen, Norway

<sup>6</sup>London School of Hygiene and Tropical Medicine, London, UK  
Correspondence to: N Bhandari  
CHRD@sas.org.in

Cite this as: *BMJ* 2014;349:g4988  
doi: 10.1136/bmj.g4988

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;349:g4988

## thebmj.com

Effect of implementation of Integrated Management of Neonatal and Childhood Illness (IMNCI) programme on neonatal and infant mortality (*BMJ* 2012;344:e1634)

Editorials: Going the last mile in child survival in India (*BMJ* 2014;349:g5222)

## STUDY QUESTION

What is the effect of implementation of the Integrated Management of Neonatal and Childhood Illness (IMNCI) programme on treatment seeking practices for morbidities in infants?

## SUMMARY ANSWER

Implementation of IMNCI, which includes home visits for newborn care and training health workers in case management of childhood illnesses, was associated with timely treatment seeking from appropriate providers and reduced morbidity.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Home based newborn care interventions have shown improvement in newborn care practices, and IMNCI implementation in Haryana, India, reduced infant mortality by 15%. The IMNCI intervention implemented at scale is effective in improving treatment seeking from appropriate providers and reducing neonatal and infant morbidities.

## Design

This was a cluster randomised controlled trial.

## Participants and setting

We included 29 667 births in nine intervention clusters and 30 813 births in nine control clusters (total population 1.1 million) in Haryana, India.

## Primary outcome(s)

Treatment seeking practices was a pre-specified outcome. Morbidity, hospital admissions, post-neonatal infant

care, and nutritional status outcomes were reported from retrospective exploratory analyses.

## Main results and the role of chance

Treatment was sought more often from an appropriate provider for severe neonatal illness (risk ratio 1.76, 95% confidence interval 1.38 to 2.24), local neonatal infection (4.86, 3.80 to 6.21), diarrhoea at 6 months (1.96, 1.38 to 2.79) and 12 months (1.22, 1.06 to 1.42), and pneumonia at 6 months (2.09, 1.31 to 3.33) and 12 months (1.44, 1.00 to 2.08). Treatment seeking within 24 hours was significantly higher for severe neonatal illness (risk ratio 1.14, 1.10 to 1.18), local neonatal infection (1.97, 1.71 to 2.27), and pneumonia at 6 months (1.31, 1.16 to 1.48). Infants in the intervention group were more likely to be exclusively breast fed in the sixth month of life (risk ratio 3.19, 2.67 to 3.81). Intervention mothers reported fewer episodes of severe neonatal illness (risk ratio 0.82, 0.67 to 0.99) and lower prevalence of diarrhoea (0.71 (0.60 to 0.83) and 0.63 (0.49 to 0.80)) and pneumonia (0.73 (0.52 to 1.04) and 0.60 (0.46 to 0.78)) in the two weeks and hospital admissions in the three months preceding the interviews at 6 and 12 months, respectively.

## Harms

No harms of the intervention were reported.

## Bias, confounding, and other reasons for caution

After randomisation, some differences in population characteristics existed between intervention and control clusters, but the effects were adjusted for these confounders. Independent teams measured outcomes, but the teams may not have been totally blind to the intervention.

## Generalisability to other populations

The results of this study are generalisable to similar rural and semi-urban populations in settings where recognition of infant morbidities requiring treatment and treatment seeking from appropriate sources is suboptimal.

## Study funding/potential competing interests

The study was funded by the World Health Organization, Geneva (through an umbrella grant from USAID); the United Nations Children's Fund, New Delhi; and the GLOBVAC Program of the Research Council of Norway.

## Trial registration number

Clinical trials NCT00474981; ICMR Clinical Trial Registry CTRI/2009/091/000715.

Effect of intervention on treatment seeking practices during infancy. Values are numbers (percentages) unless stated otherwise

Treatment seeking practices	Intervention clusters	Control clusters	Risk ratio (95% CI)
<b>Danger signs in neonatal period</b>	<b>(n=1010)</b>	<b>(n=1269)</b>	
Sought treatment within 24 hours of illness recognition	805 (79.7)	874 (68.9)	1.14 (1.10 to 1.18)
Sought treatment from appropriate provider	474 (46.9)	374 (29.5)	1.76 (1.38 to 2.24)
<b>Local infections in neonatal period</b>	<b>(n=996)</b>	<b>(n=1100)</b>	
Sought treatment within 24 hours of illness recognition	474 (47.6)	278 (25.3)	1.97 (1.71 to 2.27)
Sought treatment from appropriate provider	577 (57.9)	138 (12.5)	4.86 (3.80 to 6.21)
<b>Pneumonia at 6 months (2 weeks before interview)</b>	<b>(n=269)</b>	<b>(n=375)</b>	
Sought treatment within 24 hours of illness recognition	198 (74)	217 (58)	1.31 (1.16 to 1.48)
Sought treatment from appropriate provider	72 (27)	56 (15)	2.09 (1.31 to 3.33)
<b>Diarrhoea at 6 months (2 weeks before interview)</b>	<b>(n=642)</b>	<b>(n=866)</b>	
Sought treatment within 24 hours of illness recognition	334 (52.0)	420 (48.5)	1.10 (0.94 to 1.29)
Sought treatment from appropriate provider	146 (22.7)	106 (12.2)	1.96 (1.38 to 2.79)

# Genetic contribution to postpartum haemorrhage in Swedish population: cohort study of 466 686 births

Anna Sara Oberg,<sup>1,2</sup> Sonia Hernández-Díaz,<sup>1</sup> Thomas Frisell,<sup>3</sup> Michael F Greene,<sup>4</sup> Catarina Almqvist,<sup>2,5</sup> Brian T Bateman<sup>6,7</sup>

## EDITORIAL by Chong and colleagues

<sup>1</sup>Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA

<sup>2</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO-box 281, S-171 77 Stockholm, Sweden

<sup>3</sup>Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital, Eugeniahemmet T2, S-171 76 Stockholm, Sweden

<sup>4</sup>Department of Obstetrics and Gynecology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

<sup>5</sup>Astrid Lindgren Children's Hospital, Lung and Allergy Unit, Karolinska University Hospital, S-171 76 Stockholm, Sweden

<sup>6</sup>Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA

<sup>7</sup>Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA  
Correspondence to: AS Oberg  
oberg@hsp.harvard.edu

Cite this as: *BMJ* 2014;349:g4984  
doi: 10.1136/bmj.g4984

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;349:g4984

## STUDY QUESTION

Does postpartum haemorrhage cluster in families and to what extent can any clustering be explained by known risk factors or shared genetic and environmental effects?

## SUMMARY ANSWER

Postpartum haemorrhage clusters within women (with same and new partner) and sisters, and sharing of known risk factors explains only a small fraction of the clustering. About two thirds of the variation in postpartum haemorrhage is attributable to factors shared in families, the largest fraction being fixed maternal factors (genes and environment explaining 18% and 10% of the total variation, respectively).

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Postpartum haemorrhage is a leading cause of maternal morbidity and mortality. This study suggests there is a genetic predisposition to this serious complication of delivery.

## Participants and setting

Population register study linking the Swedish medical birth register and multi-generation register.

## Design, size, and duration

The first two live births occurring to individuals in Sweden between 1997 and 2009 contributed to six principal family relations in which the clustering of postpartum haemorrhage (defined as >1000 mL estimated blood loss) was assessed. The number of births included in analysis restricted to vaginal deliveries was 307 756.

## Main results and the role of chance

The prevalence of postpartum haemorrhage after vaginal delivery was 4.6%. Cluster correlations were most pronounced within women (same or separate partner), with small significant correlations also seen in sister and brother pairs. Inclusion of covariates in alternating logistic regression models showed that sharing of known risk factors explained only a small fraction (10%) of the clustering (nearly all influence attributable to high birth weight). Lastly the observed cluster correlations were used to quantify the relative contributions of genetic and environmental effects to the total variation in postpartum haemorrhage liability. Shared maternal factors explained most of familial clustering, with 18% (95% confidence interval 9% to 26%) of the total variation attributed to maternal genetic factors

## Familial clustering of postpartum haemorrhage associated with vaginal delivery; tetrachoric correlations

Family relationship (type of cluster)	No of pairwise correlations	Correlation coefficient (95% CI)
Couples	116 552	0.36 (0.34 to 0.38)
Mothers, new partner	21 090	0.29 (0.24 to 0.35)
Fathers, new partner	16 236	0.00 (−0.07 to 0.07)
Sisters	63 352	0.10 (0.06 to 0.13)
Brothers	57 332	0.05 (0.02 to 0.09)
Mixed siblings	112 420	0.01 (−0.02 to 0.03)

and 10% (1% to 19%) to unique maternal environment. Fetal genetic effects were estimated to explain 11% (0% to 26%). Nearly three fifths of the variation in postpartum haemorrhage could not be explained by factors shared in families (suggesting non-shared environment substantially contributes to the risk for the complication). Inclusion of caesarean deliveries (full sample 466 686) did not change the findings materially.

## Bias, confounding, and other reasons for caution

Studies suggest blood loss is routinely underestimated in the delivery setting. Assuming that the diagnosis of postpartum haemorrhage is applied with high specificity (expected as underestimation of blood loss is far more likely than overestimation), non-differential misclassification of the outcome would, if anything, bias our estimates of familial clustering to the null. These analyses are confined to a subset of the population (first two births among those with at least two births). The overall prevalence of postpartum haemorrhage, however, was similar to that in the source (general) population in the study period.

## Generalisability to other populations

The source population for the cohort includes all live births in hospital in Sweden, but the extent to which these findings generalise to other populations will need to be established. In particular, shared genetic and environmental contributions might be different in settings where birth is not medicalised and women are not exposed to drugs like oxytocin or other obstetrical interventions.

## Study funding/potential competing interests

The study was funded by the Swedish Research Council, the strategic Research Program in Epidemiology at Karolinska Institutet, and the National Institutes of Health. SH-D has received fees from consulting from Novartis and GSK.