Abstracts

Aspirin and cardiovascular events in diabetics

Aspirin is widely prescribed to diabetics with the aim of preventing cardiovascular events. However, existing guidelines are based on indirect evidence taken from large trials of populations at high risk of cardiovascular events. There is little evidence supporting the use of aspirin in populations of diabetics only.

A meta-analysis (287 trials, 135 000 participants) on the efficacy of antiplatelet therapy in the prevention of major cardiovascular events found a clear benefit of aspirin overall, but no statistically significant benefit in the subgroup of people with diabetes only (9 trials, 5 126 participants). No significant reduction in the risk of major cardiovascular events with low-dose aspirin compared with placebo was found in 3 additional trials published after the meta-analysis.

Reactions of many in the scientific and clinical community to the results of the most recent trials have been mixed, some arguing for definite proof of the lack of aspirin's efficacy in the primary prevention of cardiovascular events, others raising claims that data are still inconclusive and more trials are warranted. The persisting uncertainties form the basis of this meta-analysis of trials on the benefits and harms of aspirin in people with diabetes and no pre-existing cardiovascular disease.

The authors used Medline (1966 - November 2008), the Cochrane central register of controlled trials (*Cochrane Library* 2008; issue 4), and reference lists of retrieved articles.

They compared randomised trials of aspirin with placebo or no aspirin in people with diabetes and no pre-existing cardiovascular disease. Data on major cardiovascular events (death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, and all-cause mortality) were extracted and pooled with a random effect model. Results are reported as relative risks with 95% confidence intervals (CIs).

Of 157 studies in the literature searches, 6 were eligible (10 117 participants). When aspirin was compared with placebo there was no statistically significant reduction in the risk of major cardiovascular events (5 studies, 9 584 participants, relative risk 0.90, 95% CI 0.81 - 1.00); cardiovascular mortality (4 studies, *N*=8 557, 0.94, 0.72 - 1.23); or all-cause mortality (4 studies, *N*=8 557, 0.93, 0.82 - 1.05). Significant heterogeneity was found in the analysis for myocardial infarction (I^2=62.2%, *p*=0.02) and stroke (I^2=52.5%, *p*=0.08). Aspirin significantly reduced the risk of myocardial infarction in men (0.57, 0.34 - 0.94), but not in women (1.08, 0.71 - 1.65, *p* for interaction=0.056). Evidence relating to harms was inconsistent.

A clear benefit of aspirin in the primary prevention of major cardiovascular events in people with diabetes remains unproved. Sex may be an important effect modifier. Toxicity is to be explored further.

De Berardis G, *et al. BMJ* 2009; 339: b4531 (doi:10.1136/bmj.b4531).

Interventions to prevent sepsis-related neonatal deaths

There are about 900 000 sepsis-associated neonatal deaths per year in developing countries, mainly in the first week of life. The fact that sepsis occurs so early provides particular opportunities to prevent intrapartum and vertical transmission of bacteria to neonates. For example, widespread use of targeted prophylaxis with intrapartum antibiotics in the USA coincided with a 70% reduction in early-onset group B streptococcal disease. However, this approach is not possible in developing countries. The increased diversity of sepsis-causing pathogens in developing countries also suggests that there is potential value in a syndrome-based rather than pathogen-specific approach to prevention. Maternal deaths are also increased in developing countries, with about half of the 500 000 deaths per year arising in sub-Saharan Africa.

Intravaginal washes during labour with chlorhexidine, a commonly available wide-spectrum microbicide, have been proposed as a cheap, simple, and accessible intervention that could potentially reduce neonatal and maternal postpartum sepsis in developing countries. Vaginal washes with intrapartum chlorhexidine are thought to reduce neonatal sepsis by preventing newborn acquisition of bacteria that colonise the mother's vagina during labour and delivery. Chlorhexidine is safe and well tolerated as a vaginal cleanser in pregnant women in solutions of up to 1% concentration and in solutions of up to 4% as a cleanser for the newborn umbilical cord.

In 2 non-randomised studies in Africa, use of chlorhexidine wipes to clean the birth canal and newborn baby was associated with significant reductions (50 - 75%) in neonatal and maternal sepsis-associated morbidity and neonatal mortality. However, the conclusions drawn from reviews about the use of chlorhexidine for cleansing the maternal vaginal canal and newborn skin are that a randomised controlled trial, preferably done in a developing country, is needed before this intervention is accepted globally.

In a Cochrane meta-analysis of randomised or quasi-randomised trials, vertical transmission of group B streptococcus, but not early-onset infection with this bacterium or maternal or neonatal infections caused by other pathogens, was reduced significantly by the use of chlorhexidine. This study therefore assessed the efficacy of intrapartum and neonatal chlorhexidine in reducing early-onset neonatal sepsis and vertical transmission of group B streptococcus.

In a trial in Soweto, 8 011 women (aged 12 - 51 years) were randomly assigned in a 1:1 ratio to chlorhexidine vaginal wipes or external genitalia water wipes during active labour, and their 8 129 newborn babies were assigned to full-body (intervention group) or foot (control group) washes with chlorhexidine at birth, respectively. In a subset of mothers (*N*=5 144), the authors gathered maternal lower-vaginal swabs and neonatal skin swabs after delivery to assess colonisation with potentially pathogenic bacteria. Primary outcomes were neonatal sepsis in the first 3 days of life and vertical transmission of group B streptococcus. Analysis was by intention to treat.

Rates of neonatal sepsis did not differ between the groups (chlorhexidine 141 (3%) of 4 072 v. control 148 (4%) of 4 057, *p*=0.6518). Rates of colonisation with group B streptococcus in newborn babies born to mothers in the chlorhexidine (217 (54%) of 401) and control (234 (55%) of 429) groups did not differ (efficacy –0.05%, 95% CI –9.5 - 7.9).

Because chlorhexidine intravaginal and neonatal wipes did not prevent neonatal sepsis or vertical acquisition of potentially pathogenic bacteria among neonates, we need other interventions to reduce childhood mortality.

Cutland CL, *et al. Lancet,* Early Online Publication, 20 October 2009. doi:10.1016/S0140-6736(09)61339-8.

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