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RANDOMIZED CONTROLLED TRIAL ON KANGAROO MOTHER CARE IN BOGOTÁ: COST-UTILITY ANALYSIS.

Juan G. Ruiz, Nathalie Charpak, Mario Castillo, John Ríos, Astrid Bernal, Tammy Trujillo.

Kangaroo Mother Care (KMC) use as an alternative for care in incubators at a neonatal minimal care unit has been shown to be safe, efficacious and effective in several well conducted randomized controlled trials (RCT). Nevertheless there are no published complete economic evaluations of the intervention.

The present study performs a cost-utility analysis on the results of a large RCT conducted in Bogotá, Colombia between 1993 and 1996. Resource use and health outcomes were estimated from the RCT results. Valuing of consumed resources was made by micro-costing in a convenience sample of preterm and LBW infants treated at a University Hospital in Bogotá in 2011, and at the KMC clinic of Fundación Canguro in the same period. Utility scores to health outcomes were assigned by a groups of experts using two different approaches: a) direct ordering and scoring of mutually exclusive health states, and b) constructing an additive multi-attribute utility function. Incremental Cost-Utility Ratios were constructed using cost and utilities from 592 study participants who had complete and unbiased information after 1 year of corrected age. Uncertainty was assessed by means of computing 95% CI around the ICUR (Fiellers theorem method) and by one-way sensitivity analysis on prices estimates for valuating costs.

Estimated ICUR was Col$ -2'783.236 per extra QALY gained using the KMC method (95% CI Col$-14'333.117 to Col$ 8'838,754).

In summary, in Bogotá Colombia, the use of KMC for caring for stable preterm infants under 2000 g of weight at birth is not only highly cost-effective but dominant (more effective and cost-saving). Although results from an economic analysis are not extrapolable due to differences in cost structures between societies, a clearly dominant result strongly suggest that KMC could be cost-saving in many countries and societies.

EXECUTIVE SUMMARY.

1. RATIONALE

LBW is a major public health problem worldwide, but the burden represented by this condition is considerably higher in developing countries. Currently in Colombia, about 11% of all live newborn infants are under 2500 g. at birth. In 1993, (the time when the randomized controlled trial of interest for the present paper was started) at the largest obstetric social security facility in Bogotá, 25% of all

live deliveries corresponded to infants with birth weight ≤2500g and 10% ≤ 2000 g.

Proper health care of these infants requires access to expensive and sophisticated technology as well as highly qualified health care professionals. The economic burden related to neonatal care of low birth weight infants is very high and this is a cause for concern even in scenarios with easy access to health care resources. In resource-restricted scenarios the problem is even greater. Scarcity of resources makes it imperative to attempt to prevent LBW deliveries and to provide humane, efficacious and efficient care to all LBW infants, despite the enormous inequalities in the access to the necessary resources. Interventions claiming to address these problems must be scientifically evaluated in terms not only of efficacy, effectiveness and safety but also in terms of efficiency, feasibility and affordability. Kangaroo Mother Care (KMC) is one of those alternatives proposed to address some of the multiple problems and dimensions that need to be confronted when providing neonatal care to LBW and premature infants.

KMC was originally developed as an alternative to standard hospital care for stable LBW infants who had already overcome major adaptation problems to extrauterine life and whose main physiological need was the provision of a neutral thermal environment to allow them to thrive properly. Neutral thermal environment is provided using incubators while the infant receives inpatient care at an intermediate or minimal care neonatal unit. Inpatient or ambulatory KMC was proposed as an alternative to incubator at a minimal care unit. Since the original description, the KMC intervention methods, therapeutic goals and the range of scenarios in which KMC is used have evolved and expanded considerably.

The cornerstone of KMC is the so-called kangaroo position: continuous skin-to-skin contact between the mother and her baby. The other main two components of the intervention are nutrition based on breastfeeding and timely (early) discharge with close and careful ambulatory follow-up.
In 1993, our group started a randomized clinical trial comparing KMC and "traditional" care. Data collection ended in December 1996. Infants were followed from birth to eligibility to KMC, and were randomly assigned to KMC or to "traditional care" in incubators.

Participants were followed up to 12 months of corrected age. Clinical trial results showed that kangaroo infants did at least as good of even better than babies under usual care. After this study, KMC was gradually accepted as the standard of care in Colombia.

The provision of KMC implies changing the patterns of health care provision and probably changing the costs of care. A priori, early discharge from hospital (which is a policy in KMC) is expected to reduce health care costs. On the other hand, providing KMC also consumes resources and the costs of production have not been clearly identified. In addition, health outcomes differ between KMC and "traditional care" in incubators. In order to understand whether KMC estimated benefits are worth the cost, a formal economic evaluation should be performed.

A complete economic evaluation should enumerate and value all the health effects attributable to an intervention. It also enumerates and values all the resources used or saved when delivering the health care intervention. Then it tries to compare both costs and outcomes in a meaningful way and offers an estimation of whether the benefits are worth the resources invested and the risk incurred. The merits and costs are always estimated by comparison with a standard or control intervention. Incremental benefits and costs are compared, i.e. differences in costs and effects between competing interventions.

In the literature there are no reports of a complete economic evaluation of KMC. The existence of detailed experimental (unbiased) data on effects and on patters of resource use collected during the 1993-1996 KMC randomized controlled trial offered a unique opportunity to perform a cost-utility evaluation of the KMC method as an alternative to minimal inpatient care for stable preterm and LBW infants.

2. OBJECTIVE

To perform a complete economic evaluation (cost-utility analysis) for estimating the incremental cost-utility ratio (ICUR) of KMC as compared to neonatal inpatient care at a minimal care unit (incubators).

3, METHODS

1. The original Randomized Controlled Trial (RCT)

Between 1993 and 1996 an open randomized controlled trial was conducted with the objective of estimating effectiveness and safety of KMC as compared to "traditional" care in LBW infants in terms of overall mortality, infectious morbidity, growth and development, total length of hospital stay and duration of breast-feeding during the first year of corrected age. Secondary objectives included the description of the quality of the mother-to-infant bonding. The study was conducted at the largest Colombian Social Security Institute (ISS) tertiary care Hospital in Bogotá, able to provide neonatal intensive care. The ambulatory component of KMC was developed and evaluated at the ISS high-risk neonate clinic.

Study participants were newborn infants under 2000 g at birth, who survived the neonatal period and who were eligible for an in-patient minimal care unit (MCU); 1084 consecutive deliveries of infants under 2000 g were followed and 746 were randomized, 382 were allocated to KMC and 364 to control. Information on 693 participants (93%, including 30 demises) was available at one year, and the present economic evaluation was conducted on them.

KMC infants were discharged as soon as they were randomized, regardless of weight or gestational age. Infants were kept 24 hr/day in an upright position, in skin-to-skin contact and firmly attached to

the mother's chest until KMC wasn't tolerated anymore. Control babies were kept in incubators at the MCU until they satisfied usual discharge criteria. Both groups were followed at term and at 3, 6, 9 and 12 months of corrected age.

Main outcome measures included mortality, infectious episodes, and total length of hospital stay, growth and development, sequels and proportion of breast feed infants; and most baseline variables were evenly distributed, except for weight at recruitment (KMC=1678 control=1713, p=0.045).

Risk of dying was lower for KMC infants at all points in time during the follow up period although differences in mortality were not significant: at twelve months there were 11 deaths out of 350 infants -3.0%- in Kangaroo and 19 deaths out of 343 -5.5%- in the control group, for a risk ratio control versus kangaroo of 1.76 (95%CI 0.85-3.7). After controlling for potential effect modifiers by means of logistic regression, the OR increased up to 1.96 (0.96-3.92). Cox regression yielded almost identical results. Multivariate logistic regression showed that most of the variance observed in mortality was explained by a model containing the educational level of the father as a proxy for global SES and educational factors; weight at eligibility, accounting for the mixed influence of all biological events prior to eligibility and the experimental exposure (Kangaroo infants doing better).

There were no differences in growth indices (height, weight and head circumference expressed as proportion of expected value for corrected age) up to the age of 12 months except for head perimeter. After the age of 3 months, head circumferences were statistically significantly larger in kangaroo infants, even after controlling for potential effect modifiers (gender, educational level of the mother, SES status, observed/expected head circumference at birth, weight and gestational age at eligibility).

Proportions of mothers who breastfed their infants were higher in the kangaroo group up to the age of three months. Afterwards, the differences disappeared, probably in association with the return of most mothers back to work, after the legal 3 months maternity absence of leave.

Kangaroo infants, especially those weighting under 1800 g at birth spent less time in hospital, this difference was maintained up to year of corrected age and was statistically significant in each point of follow up.

Frequency of infectious episodes was similar, although the spectrum and the severity were different between the survivors in the two groups. Control infants had a higher cumulative incidence of severe infections, requiring admission to hospital. In addition, they presented a higher proportion of nosocomial infections between eligibility and the first visit at 41 weeks of PCA.

2. The economic evaluation: assumptions and methods.

2.1 Study design:
This is a cost-utility (a variant of a cost-effectiveness) evaluation of an intervention based on the results of an RCT. Although the economic evaluation was not conducted in parallel with the study, the basic approach is that of an economic evaluation conducted within an RCT instead of an economic model.

2.2 Study Population
Same as the study population of the original KMC RCT: preterm or LBW infants with birth weight under 2000 g who survived the neonatal immediate transition and who were eligible for initiating KMC while in hospital. Severe birth asphyxia, early severe neurological sequels, major or lethal malformations are excluded. The estimation is conducted in 592 infants who had complete and unbiased information on both resource use and health related outcomes at one year of corrected age.

2.3 Perspective
The economic analysis is conducted from the point of view of the Colombian Social Security system, which pays for health care related expenses (hospital, ambulatory care, tests, medications, interventions, etc.), and also pays for maternity leave.

2.4 Time horizon: From eligibility to 1 year of corrected age.

2.5 Currency, costs and discount rate:
Use of resources is valuated in Colombian $ of 2011. Resource use was recorded in the RCT in terms of health care episodes: visits, days of hospital stay in different levels of complexity (intensive, intermediate or minimal neonatal care, general pediatric Ward, pediatric intensive care), visits due to infectious episodes requiring ambulatory courses of antibiotics, re-admissions to hospital. Costs of hospital stay (average cost per day) were estimated trhough an specific valuation of resource use during hospital stay in a convenience sample of 57 preterm infants less that 2000 g cared for at Hospital Universitario San Ignacio in Bogotá during 2011, for both primary neonatal hospitalization and neonatal and pediatric readmissions (infectious episodes) during the first year of age. Micro-costing was used for identifying average resource use per hospital-day (detailed billing records). Valuation of resources consumed was made using standard pricing lists from the Colombian Ministry of Health (ISS+30%). When data were not available, average purchasing cost from San Ignacio Hospital records (2011) was employed. Ambulatory KMC resource use and valuation came from detailed cost-structure files kept by the "Programa Madre Canguro Integral" run by Fundación Canguro at San Ignacio Hospital during 2011.

Measured costs included differential costs for producing the interventions (health sector costs, the so-called "direct medical costs") and cost of treatment of not avoided complications and disease

events (so-called "induced costs"). Costs attributable to unrelated health events (for instance surgical correction of inguinal hernia, or treatment of hip dysplasia, etc.) were not taken into account. Out of the pocket family expenses and productivity losses were not included.

Given that time horizon was limited to one year, no discount rates were employed.

2.6 Utilities

Two alternative approaches were used to estimate utilities from the RCT results: a) direct ordering and scoring of health outcomes, and b) constructing a multi-attribute utility function. For both procedures, all relevant recorded outcomes were examined and classified in three domains: a) Disease-related outcomes (mortality, infectious episodes, medical events and complications, sequels), b) health-related outcomes (growth indices, neuromotor development and integrity, breast-feeding patterns) and c) performance and quality of life-related outcomes (developmental scores, mother-infant bonding and attachment, home environment). Information was not interpretable against a population reference for all outcomes measured. In consequence, not directly interpretable data such as bonding test results, attachment and home environment, although different between groups, could not be scored for utility and were excluded.

For assigning utility values, a group of 8 expert neonatal and infant care providers (neonatologists and pediatricians) was consulted.

In developing the first alternative for assigning utilities (direct ordering and scoring of outcomes), disease-related, health related and quality of life related outcomes were categorized and all possible patterns of covariance in the studied population were assembled. The number of mutually exclusive discrete health states was reduced to 9 clearly distinct categories, which were ordered by the consulting experts according to perceived utility. Anchor points were "perfect health" for a premature infant at 1 year (utility of 1) and death or health states similar to death (severe neurological and physical sequels, severe handicap, poor general health, utility 0). Using a modified Delphi process, each state was assigned a score by each expert; averages were fed-back to experts who revised their scores in the light of average scores. After two rounds, average scores were produced and consensus on each individual score was documented.

For the second alternative (Multi-attribute utility function), an additive utility function model was chosen. The Swing Weighting method (Clemen 1996) was used, to assign scores to each outcome variable by each expert. Absolute scores, relative weights and performance scores for each participant in each variable were produced. Solving the multi-attribute function equation for each participant produced a utility score from 0 to 1.

2.7 Cost-utility ratios.

Incremental cost-utility ratios (ICUR) were computed comparing costs and effects between kangaroo

and control study participants. ICUR estimates from the two methods for estimating utilities were computed and compared (see sensitivity analysis). The ICUR is the ratio of the average difference in cost between kangaroo and control infants and the average difference in utility. Utility scores were employed as quality-of-life weights for estimating Quality adjusted life years (QALY). Given that these scores represented the utility of the health state at which each participant was at one year of corrected age, number of QALYs were obtained by multiplying the follow-up time form eligibility to the end of follow up (for survivors, 1 year of corrected age; for demises, time from eligibility to death) times the assigned utility score.

2.8 Uncertainty and sensitivity analysis

The main and more relevant source of uncertainty in the present evaluation (economic analysis of a RCT) is sampling variation (random error). Sampling uncertainty was evaluated by computing 95% confidence intervals around the point estimate of the ICUR, using the Fieller theorem (Glick, et. al. 2011). Effects of variation in estimating utilities were assessed by one-way sensitivity analysis employing two different procedures for deriving utilities, as described before. Effects of variation in valuing the consumed resources were assessed by one-way sensitivity analysis of costs, employing maximum, minimum and average prices for valuating resources.

4. RESULTS

After applying strict inclusion and exclusion criteria, a total of 592 subjects with complete information were included in the analysis. Baseline characteristics were not statistically or clinically significantly different from those of the originally recruited sample of 746 infants. In addition, main potential confounders and demographic variables were similarly distributed between kangaroo and control infants.

Average utility (QALYs) using the Multi-attribute utility function was 0.84 QALY per infant. In the kangaroo group utility was 0.876 QALY per infant and in the control there were on average 0.809 QALY per infant. This difference is statistically significant ($p < 0.001$). Comparable results are obtained using the direct ordering and scoring approach: in kangaroo infants 0.846 QALY per infant vs. 0.78 QALY per infant in the control group.

Average differential costs were Col$ 2'810,531 for kangaroo infants and Col$ 2'997,643 for control infants, and the difference is not statistically significant ($p=0.12$). The size and direction of the difference did not varied using maximum or minimum estimations of costs.

The utility estimated by means of the multi-attribute function was used as the baseline case scenario for estimating the ICUR: Col$ -2'783,236 per additional QALY gained by kangaroo infants. A negative ICUR means that the kangaroo method alternative is DOMINANT: is less expensive and more effective. It can be interpreted as saving on average Col$2.7 million per additional QALY gained per KMC

treated infant.

The Fiellers 95%CI varied from Col$ -14'333,117 to Col$ +8'838,754, which means that due to sampling variation, one can be 95% confident that using KMC can be clearly dominant and cost-saving: saving more that Col$ 14 million per additional gained QALY. On the other side of the 95%CI, KMC is not dominant and one could be expending a bit less that Col$ 9 million in order to gain an additional QALY.

This upper limit of the interval estimation falls clearly under the estimated threshold for cost-effectiveness in Colombia, where willingness to pay per gained QALY is up to Col$ 36 million (about US$18.000 per gained QALY).

5. CONCLUSION

KMC employed as an alternative to care in incubators at a MCU for stable LMW infants with weight at birth under 2000 g, according to cost structure in Bogotá Colombia, is clearly an efficient intervention. Point estimate of ICUR shows that Kangaroo is dominant, with savings of 2.7 million pesos per QALY gained per infant. In other words is more effective and less costly. Sensitivity analysis shows that, in the worst-case scenario, one can be 95% confident that it is clearly cost-effective. The amount paid per extra QALY gained (8.9 million pesos) falls clearly under the Colombian threshold for cost-effectiveness, which is Col$ 36 million per gained QALY.

Although results from an economical evaluation cannot be extrapolated due to differences in cost structures between different populations, this clearly dominant result strongly suggests that KMC can be cost-effective in many other societies and countries.

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Juan Gabriel Ruiz Peláez, MD MMedSci
Titular Professor,
Departments of Pediatrics & Clinical Epidemiology,
School of Medicine, Pontificia Universidad Javeriana
and Senior Researcher & Scholar, Fundación Canguro
Bogotá, Colombia.

Dr. Juan G. Ruiz is currently an attending pediatrician at the San Ignacio University Hospital in Bogotá, Colombia, where he is also professor of Clinical Epidemiology and of Pediatrics at the School of Medicine, Pontificia Universidad Javeriana. In addition he is a founding member and major responsible for research of the Fundación Canguro, in Bogotá Colombia. He has been the co-director of the Clinical Epidemiology and Biostatistics Unit and Chair of the Department of Pediatrics at the School of Medicine, Pontificia Universidad Javeriana.

Dr. Ruiz received his M.D. from the Pontificia Universidad Javeriana, Faculty of Medicine, Bogotá, DE Colombia in 1980, following the completion of a 7 years M.D. program. After serving 1-year medical social service in the rural area of Cundinamarca, Colombia, he trained from 1981 through 1984 in Pediatrics at the San Ignacio University Hospital. He obtained his Masters degree in Clinical Epidemiology at the Asian & Pacific Centre for Clinical Epidemiology & Biostatistics, Faculty of Medicine, University of Newcastle, Newcastle, NSW, Australia, in 1990 and received further training in Clinical Economics and Clinical Decision Analysis at the Center for Clinical Epidemiology & Biostatistics, University of Pennsylvania, School of Medicine, in Philadelphia, PA, in 1996. Since 1989 he has been the PI and co-PI of several epidemiological and clinical studies, mainly in the area of appropriate care of preterm and low birth weight infants. In 1994 with several research colleagues he founded the Fundación Canguro in Bogotá, an NGO devoted to research, teaching, training and direct medical care related to Kangaroo Mother Care (KMC) method for premature infants, that besides conducting large clinical trials on KMC has been actively disseminating the technique mainly in low and middle income countries in Latin America, South East Asia, India, Africa and Eastern Europe. In 1996 in Trieste, Italy he was among the group of international researchers, physicians and nurses who founded the International Kangaroo Network –INK-, an international alliance devoted to collaborating in enhancing and disseminating the Kangaroo Mother Care (KMC) method.

Dr. Ruiz continues to work as an attending pediatrician and a clinical epidemiologist and his current main research interest is in integrative methods for summarizing and putting into action what is known about of KMC, in the form of evidence-based clinical practice guidelines and economic analyses. He is also involved in conducting evaluations of long-term (adolescents) neurodevelopment outcomes in former preterm infants exposed to KMC.