

What Have We Learned from the Study on Melamine: A Personal Sentiment on Conducting Clinical Studies

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In September 2008 there was an outbreak of childhood urinary stones induced by melamine-tainted milk formulae. The Chinese paediatricians and paediatric nephrologists devoted their effort and hard work immediately to screen a large number of children exposed to melamine-tainted milk for renal stones, obstruction of the urinary tract and impaired renal function. Paediatricians also initiated studies on the clinical aspects and the pathogenesis of melamine related stones. Through this conjoint research effort, we found that (1) children exposed to high melamine formula were seven times more likely to have urinary stones as compared with those not exposed; (2) most children were asymptomatic and seldom had symptoms such as oliguria, crying on urination, oedema or history of passing out stones; (3) symptoms did not distinguish children with urinary stones from those with suspected stones or without stones; (4) infants and children who were born preterm were 4.5 times more likely to have stones as compared to those who were born at term.¹

From the study on melamine related urinary stones in children, for the first time we learned of the relationship of melamine exposure in infant formulae, the occurrence of urinary stones and the clinical aspect of melamine related stones in humans. It was particularly difficult for clinicians in China to conduct good quality clinical studies on the clinical characteristics of children affected by melamine related urinary stones because they were already overwhelmed by the dramatic increase in children coming

to the hospitals seeking for screening and treatment. Therefore, despite they had ample clinical experience on managing such patients, clinicians from Mainland China had made less of a contribution to the scientific literature on melamine related urinary stone. Nevertheless, we would like to summarise our experience and highlight the lessons we have learned in conducting clinical studies in China.

Melamine related urinary stone was a largely unknown disease in humans before this outbreak, and both laboratory and clinical research are essential. What were the clinical features? What was the pathogenesis? Was there correlation between the different infant formulae and severity of renal damage due to melamine related stones? What are the other risk factors associated with severe illness? The very essential and primary step for clinical study is a well planned scientific protocol, designed to answer some or all of the above research questions. These have to be planned early by clinicians and scientists experienced in clinical and epidemiological research methodology so that the protocol could be implemented without hindrance. Unfortunately, the opportunity for performing clinical study is often lost due to the time it takes to recognise the outbreak, and the need for clinicians to devote a lot of their time to handle the sudden surge of an unexpected clinical problem. During the melamine related urinary stone outbreak, clinicians in various hospitals in China had a lot of first-hand experience in treating their patients. However, good scientific evidence could not be gathered because there was initially no well designed protocol to effectively and systematically collect important relevant clinical data and samples from all patients to answer the above research questions.

There were other difficulties even in the later stages of the melamine related urinary stone outbreak when we had established a good study protocol. Implementation of the clinical study protocol was a crucial and difficult step. Even a well-designed clinical study would be hampered by incomplete implementation. Sometimes a study protocol

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might be too ideal to practise in real life situations. Doctors might need to adjust and modify it according to their own clinical work habit and workload, or try to merge the study process into their daily medical service. Another problem was the introduction of biases during execution. The study depended on competent technical skills of technicians and accurate laboratory analysis and these could be subject to bias. For example, the staff involved in ultrasound examination and laboratory testing of patients should be "blinded" to the patient's history of melamine exposure. Quality control on the questionnaire used to collect clinical information on patients affected by melamine related stones could also be performed daily. We had to admit that because of the extremely heavy workload of our clinical service, it was difficult to follow meticulously a clinical study protocol thus affecting the quality of the study results. The investigators need to be well trained in advance in order to carry out the research study with a scientific and ethical approach.

Compared with bench research (basic science study), a study at the bed-side (clinical study) will rely much more on the team work. One of the reasons of relying on team work is that clinical research on human subjects involves different procedures including diagnosis, treatment or prevention of diseases, and frequently involves many other health care professionals. Taking the study on melamine related urinary stones as an example, the entire study cannot be accomplished without the proper coordination of many departments and disciplines including paediatric nephrology and

urology teams, the nurses, ultrasonographers, laboratory staff, and clinical epidemiologists and medical statisticians. Multicentre studies would need another level of good collaboration between investigators of different hospitals and could offer larger patient population and more generalisable research findings.

Last but not least I would like to stress that more clinical studies should be conducted in China. China has a large population with a huge disease burden and potential for outbreaks of new diseases. From our experience with study on melamine related urinary stone in 2008 and the outbreak of Severe Acute Respiratory Syndrome in 2003, doctors in China were at the forefront and would be able to contribute a lot of clinical data to the medical literature, if we had established good and well trained research teams. Furthermore we need good study design, efficient implementation and collaboration among different disciplines and different hospitals to ensure success of any future research project. Our experience with melamine stone studies raised many issues of barriers but also many opportunities for clinical research. There should be more training in research methodology, clinical and epidemiological research, research ethics for young paediatricians in China.

Reference

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