Volume expansion and contrast-induced acute kidney injury

There is an ever-increasing population at risk of being exposed to intravascular iodinated contrast because of the increasingly popular practice of imaging techniques in medicine and surgery. Despite efforts to improve the safety of these agents, there has been no fundamental improvement in contrast product development since the introduction of iso-osmolar contrast more than 20 years ago.1–3 Thus, clinicians have focused on strategies to decrease the risk of contrast-induced acute kidney injury by limiting contrast volume, giving adjuvant agents, and providing supportive care once the renal damage has occurred. It has been suggested that intravascular volume expansion with isotonic crystalloid solution can decrease the incidence and the severity of contrast-induced acute kidney injury.4 This approach is attractive because the short-term administration of intravenous fluid results in an increase in renal blood flow, glomerular filtration, and increased volume of urine flow through the tubular segments of the nephron. Forced diuresis has been associated with a lesser rise in serum creatinine especially when higher rates (>150 ml/h) of urine flow have been achieved.5

In The Lancet, Estelle Nijssen and colleagues6 present the primary results from a randomised trial comparing no-hydration protocol versus prophylactic intravascular volume expansion with normal saline in a high-risk group of patients receiving contrast for radiological or cardiovascular procedures. Serum creatinine was measured after the exposure in a standard fashion. This trial was unique in that it attempted to use a non-inferiority design, which is unusual for contrast-induced acute kidney injury, setting up the hypothesis that withholding prophylaxis would be non-inferior to the standard-of-care administration of intravenous normal saline. The method of computation of the non-inferiority margin and the revision of this statistical approach was unconventional and in the end had the assumptions that the contrast-induced acute kidney injury rate in the normal saline group would be 2.4% and the rate in the no saline prophylaxis group could be as high as 4.5% with relative risk or hazard ratio of less than 1.88 to meet non-inferiority. The upper bound of the 95% confidence limit for this construction is about 4.50, which exceeds the limit for this construction is about 4.50, which exceeds this is questionable and represents an example on how clinical trials can go awry with hypothesis testing.

With the basis of clinical studies concerning volume expansion that have been published so far, how could a future trial add to our understanding of the problem and improve opportunities for patients? The first strategy is to guide the amount of intravenous fluid according to a personalised parameter such as left ventricular end-diastolic pressure or degree of total body water inferred by bioimpedance.2,5,10 Degrees of precision are needed in terms of volume expansion for renal protection with avoidance of volume overload and renal congestion (appendix). In view of the low rates of contrast-induced acute kidney injury possible in some centres and patient groups, as Nijssen and colleagues learned, all efforts to reduce variation are necessary including restriction to similar procedures, setting a standard for appropriateness, the use of iso-osmolar contrast, and measurement of approved markers of kidney damage (eg, NGAL, TIMP2*IGFBP7) to achieve greater precision on the ascertainment of contrast-induced acute kidney injury.41 We should strive for much larger trials and realistic effect sizes for interventions in the range of 20–30% risk reductions. In our view this field is not ready for non-inferiority trials until we have a reference standard intervention that is agreed upon as proven, and thus can be positioned as the control group and be compared with novel treatment or strategy.

This trial should stand as a signal to the community that attention should be shifted to large collaborative efforts that are patient-centred, rely on methods of precision medicine, and use the approved methods that allow us to better ascertain the outcome.

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