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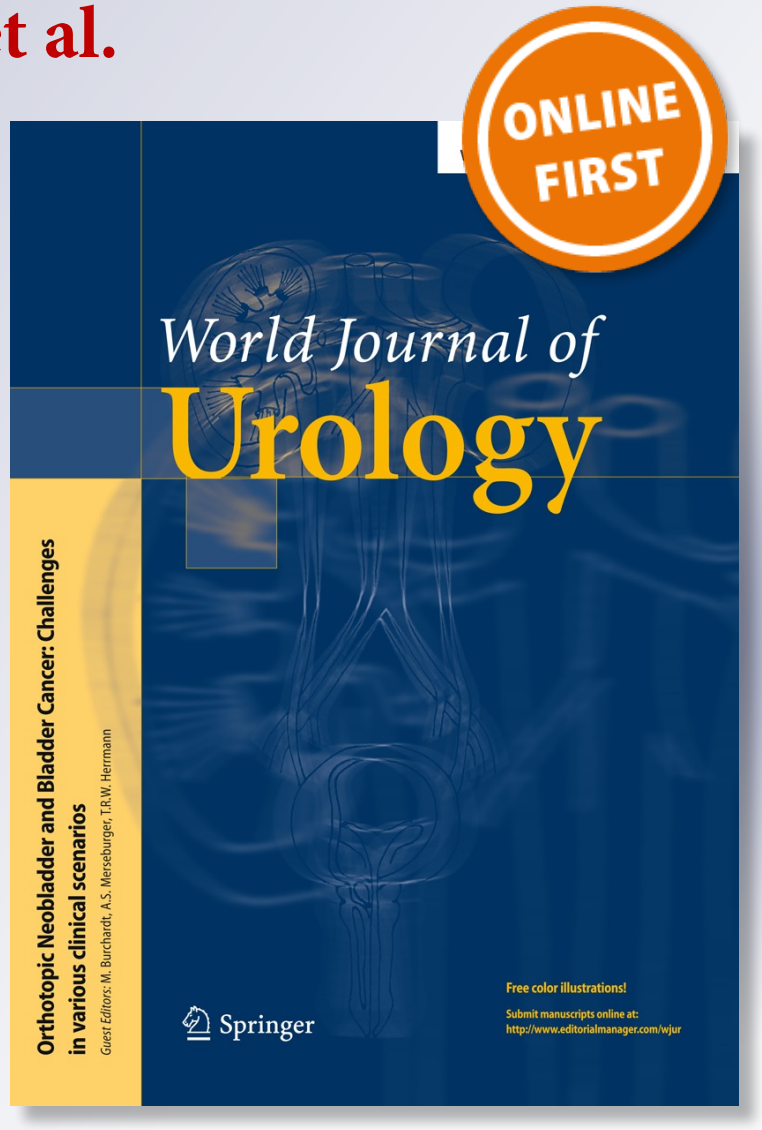

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ORIGINAL ARTICLE

The use of mannitol in partial and live donor nephrectomy: an international survey

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Abstract
Purpose Animal studies have shown the potential benefits of mannitol as renoprotective during warm ischemia; it may have antioxidant and anti-inflammatory properties and is sometimes used during partial nephrectomy (PN) and live donor nephrectomy (LDN). Despite this, a prospective study on mannitol has never been performed. The aim of this study is to document patterns of mannitol use during PN and LDN.

Materials and methods A survey on the use of mannitol during PN and LDN was sent to 92 high surgical volume urological centers. Questions included use of mannitol, indications for use, physician responsible for administration, dosage, timing and other renoprotective measures.
Results Mannitol was used in 78 and 64 % of centers performing PN and LDN, respectively. The indication for use was as antioxidant (21 %), as diuretic (5 %) and as a combination of the two (74 %). For PN, the most common

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dosages were 12.5 g (30 %) and 25 g (49 %). For LDN, the most common doses were 12.5 g (36.3 %) and 25 g (63.7 %). Overall, 83 % of centers utilized mannitol, and two (percent or centers??) utilized furosemide for renoprotection.

Conclusions A large majority of high-volume centers performing PN and LDN use mannitol for renoprotection. Since there are no data proving its value nor standardized indication and usage, this survey may provide information for a randomized prospective study.

Keywords Mannitol · Live donor nephrectomy · Partial nephrectomy · Renoprotective agent · Diuretics

Introduction

Both in living donor (LDN) and partial nephrectomy (PN), preserving renal function is crucial. It is well known that warm ischemia-time affects renal function by organ-induced ischemia and subsequent Ischemia–Reperfusion Injury (IRI). IRI is known to affect renal function which may lead to organ failure. Its biological effect lays on sub-cellular injuries with generation of free radicals leading to acute tubular necrosis, reduced glomerular filtration rate (GFR) and, eventually, renal failure [1–4]. There has been evidence that implementation of diuresis may in fact reduce the warm ischemia-related renal damage [1, 3, 5–8]. Therefore, diuretics are commonly used in partial and live donor nephrectomy. It has been speculated that mannitol may have some advantages over other diuretics due to a possible antioxidant activity [9, 10]. Despite this, there is insufficient evidence to recommend and standardize the use of mannitol.

The aim of this study is to document the trend in mannitol use during partial and live donor nephrectomy, through an international survey sent to high-volume tertiary centers.

Materials and methods

A survey on the use of mannitol during partial and live donor nephrectomy was sent by e-mail to 92 high surgical volume urological centers around the world. Survey was performed considering indications, doses and modalities of infusion and use of mannitol reported in literature. The survey was distributed and returned via e-mail in February 2011. We initially queried about the type of Institution and related surgical activities. Questions specifically related to the use of mannitol included the following: if mannitol was utilized in surgical practice, indications (partial and or donor nephrectomy), rationale of using mannitol, physician in charge for mannitol administration (urologist, nephrologist or anesthetist), dose administered in case of partial or donor nephrectomy, timing of administration (before or after clamping), usage of other type of kidney protectors and number of partial of donor nephrectomies performed per year at the corresponding Institution.

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Results

We obtained surveys from 47 centers (51 %). Forty-seven of 47 (100 %) and 17 of 47 (36 %) performed partial and live donor nephrectomy, respectively. Mannitol was used in 78.7 and 64.7 % of centers performing partial and live donor nephrectomy, respectively. The indication for mannitol use was as an antioxidant (20.5 %), as a diuretic (5.2 %) and as a combination of the two (74.3 %). The physician in charge of mannitol administration was the urologist in 53.8 % of the cases, the anesthesiologist in 30.7 % of the cases and both in 12.8 %. In case of partial nephrectomy, dosages administered were 12.5 g in 29.7 % of the cases, 25 g in 48.6 % and different dosages in 21.7 % of the cases. The timing of mannitol administration was before clamping in 75.6 % of the cases, after clamping in 5.4 % and both before clamping and at reperfusion in 19 % of the cases.

In case of live donor nephrectomy, it was administered at dosages of 12.5 g in 36.3 % of the cases and at 25 g in 63.7 %. The timing for administration was before clamping in all cases.

Overall, 83 % ($N = 39$) of the centers utilized mannitol. Of the centers not using mannitol, two utilized Furosemide as kidney protector instead of mannitol.

Discussion

Ischemia, and subsequent reperfusion injury, is a consequence of LDN and PN with arterial clamping. In both circumstances, the induced injury in the renal parenchyma is caused by the alteration of the microcirculatory compliance and by the increase in the perfusion pressure. This effect is magnified in cases of prolonged ischemia-time. Therefore, it is widely accepted that the duration of the ischemia-time is proportionally correlated with the magnitude of ischemia/reperfusion injury [2]. Although the understanding of the cell-death mechanism subsequent to ischemia/reperfusion injury has been deeply investigated during the last few years [1–3, 11], little is known about the efficacy of strategies to reduce this event during LDN and PN. Hypothermic kidney storage (ice) is the principal secure method for kidney preservation. It has been shown that hypothermia reduces cellular metabolism and slows the process that impair cell viability [1].

Diuretics have been also evaluated for kidney protection during LDN and PN. Some authors have evaluated the role of mannitol and other diuretics as kidney protector agents, and there is still a controversial opinion on its real efficacy as kidney protector agent [4, 8, 12–15]. The rationale of giving diuretics during PN or LDN is that a non-oliguric state may be maintained by promoting diuresis and protect the kidney from ischemic/reperfusion injury; furthermore, diuretics have been shown to prevent tubular obstruction, to reduce medullary oxygen consumption and to increase renal blood flow [16]. A multinational survey [14] has recently confirmed that 70 % of intensivists use loop diuretics in a large spectrum of acute renal injury conditions like major surgery, sepsis, shock, contrast or drug-induced nephrotoxicity.

Few prospective randomized trials have addressed the role of diuretics in prevention of acute renal injury, and most of them have been conducted to study the effect of contrast administration [17] and cardiac surgery [18]. Unfortunately, the results have shown that diuretics offer no protection against contrast-induced nephropathy, and in cardiac surgery, higher postoperative creatinine levels were seen in patients treated with furosemide [18]. Similar results were published in four different randomized controlled trials examining the role of diuretics in patients with established renal failure treated in intensive care unit, with no improvements reported in recovering renal function or in decreasing mortality [19–21].

Moreover, three meta-analyses published similar results and noted a significant higher risk of side effects (like hearing-loss) [13, 15, 22] for patients receiving diuretics treatment in cardiac surgery, established renal failure or contrast nephropathy. Similarly, other studies compared diuretics with dopamine or placebo without demonstrating benefits from this drug-regimen therapy [23, 24].

Mannitol is a potent osmotic fluid, with 50 g of mannitol causing an intracellular to extra-cellular shift of 1 liter of water [25]. It is metabolically inert and mostly excreted by the kidney with a minimal reabsorption (7 %) in the renal tubule [26]. Furthermore, it is known that it has a protective role against oxidative injuries acting as a scavenger of the hydroxyl radical that may result in reducing oxidant-derived injury to the kidney, heart and lung [27, 28].

In a recent review [29], results from an international collaboration of the Critical Care Nephrology Working Group of the European Society of Intensive Care medicine (ESICM), the roles of different substances used in acute renal injury were critically evaluated and, accordingly,

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recommendations for clinical practice were given. In the review, loop diuretics and mannitol were not recommended to prevent or ameliorate acute renal injury (grade 1B).

In a recent paper on mannitol use during minimally invasive partial nephrectomy, renal function outcomes were compared between patients who received i.v. Mannitol versus those who did not. Conclusions of this retrospective series were that mannitol did not influence renal function recovery and that an appropriately designed study of mannitol is needed [30].

Despite the lack of scientific evidence, our survey shows that a high proportion of surgeons both from Europe and US regularly use mannitol to protect renal function during PN and LDN (100 and 36 %, respectively); moreover, the different dosages employed at different timing during surgeries underline also the lack of standardization on its use in this setting.

Based on these findings we recently designed a prospective randomized study at our center on the use of mannitol during partial nephrectomy. All patients undergoing partial nephrectomy (open, laparoscopic or robotic) at our center will be randomly assigned to 25 g of mannitol administered as a single dose before clamping versus no mannitol. Patients will be followed postoperatively with serum creatinine, GFR and nuclear GFR at 12 h, 7 and 30 days. The study already obtained the internal ethical committee approval (IRB) and will start recruiting patients on October 15th. A second prospective randomized trial for the use of mannitol during laparoscopic live donor nephrectomy is under development.

Conclusions

Two important conclusions can be highlighted from this survey. First, the majority of the centers performing high-volume partial and live donor nephrectomy prefer to use mannitol as a kidney protector. Second, it appears that there are neither unified criteria nor standardization for mannitol indication and usage. The hope is that our ongoing prospective randomized trial will help solving the dilemma.

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Appendix: Survey

Use of mannitol in partial nephrectomy and living donor nephrectomy

Please answer the questions by adding an X to the right answer

1. Institution (Name of the Institution, City, Country)
2. Type of Institution
   a. Academic
   b. Peripheral University Affiliate
   c. Public Hospital (or County Hospital)
   d. Private Hospital
   e. Other
3. Faculty number in the department

   Number
4. Number of beds of the Urology Department

   Number
5. Is mannitol (or other similar agent) used in partial or/and donor nephrectomy at your institution?
   a. Yes
   b. No

   If you answer YES, please proceed to question 7.
   If you answer NO please proceed to question 6.
6. Reason why mannitol is not available at your institution
   a. Not part of the internal protocol
   b. Do not believe in its benefits
   c. Other
7. At your institution, mannitol is used for
   a. Partial nephrectomy
   b. Living donor nephrectomy
   c. Both
8. What is the reason of using mannitol during these surgeries?
   a. Kidney protector/Antioxidan
   b. Stimulate diuresis

c. Both
d. Other

9. Who does indicate mannitol administration?

a. Urologist
b. Nephrologist
c. Anesthetist
d. Other

In case of partial nephrectomy

10. Dosage

a. 12.5 g
b. 25 g
c. Other

11. Timing

a. Before clamping
b. After clamping
c. Other

12. Other kidney protector agent

In case of living donor nephrectomy

13. Dosage

a. 12.5 g
b. 25 g
c. Other

14. Timing

a. Before clamping
b. After clamping
c. Other

15. Other kidney protector agent
16. How many partial nephrectomies are performed at your institution per year?

a. <10
b. Between 10 and 20
c. >20
d. >50
e. >100

17. How many live donor nephrectomies have you performed at your institution?

a. <10
b. Between 10 and 20
c. >20
d. >50
e. >100

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