Lactated Ringer’s vs. normal saline solution for renal transplantation: Systematic review and meta-analysis


Abstract

Background: The administration of potassium solutions may result in hyperpotassemia during surgery; normal saline solution (NSS) traditionally used in renal transplant may cause hyperchloremic acidosis.

Objective: To compare the safety of Lactated Ringer’s (LR) against NSS in renal transplantation.

Search strategy: A systematic review was completed on Central Cochrane Registry – controlled trials, Medline, Lilacs, EBSCO and Embase, accessing review articles and contacting expert clinicians. There was no language restriction.

Selection criteria: Randomized controlled trials on adult patients undergoing renal transplantation.

Data collection and analysis: Independent trial selection, quality assessment and data extraction were performed. The mean differentials were estimated with a 95% confidence interval (95% CI). Heterogeneity was evaluated with statistic I-square (I²) and the fixed and random effect models were used.

Results: Four trials with a total of 237 patients were included. At the end of surgery, the potassium differential was non-significant (means difference (MD): −0.26 mEq/L; CI 95%: −0.58 to 0.05; p = 0.10; I² = 75%); the pH was lower in the NSS group (MD: 0.06; CI 95%: 0.05–0.08; p < 0.001; I² = 17%). No difference in Creatinine was identified on the third postoperative day (MD: −0.05; CI 95%: −0.59 to 0.48; p = 0.85; I² = 0%).
Conclusions: The use of RL vs. NSS during the renal transplantation perioperative period results in lower potassium and chloride levels and a higher pH, with no significant Creatinine changes.

© 2015 Sociedad Colombiana de Anestesiología y Reanimación. Published by Elsevier España, S.L.U. All rights reserved.
Eligibility criteria

The search included randomized, clinical controlled trials with no restrictions as to language, date or status of publication, comparing the use of LR against NSS as fluid therapy in renal transplantation patients, over 18 years old. The outcomes evaluated were the level of serum potassium, bicarbonate, chloride, Creatinine and the postoperative pH. The deadline of publication established was July 8, 2013.

Search strategies

Independently, the three authors did an electronic database search, contacting expert clinicians and searching review articles. No language and date of publication restrictions were applied.


The search terms used were “renal transplant”, “acidosis”, “acidemia”, “hyperpotassemia”, “graft dysfunction”, “Lactate Ringer’s” and “saline solution”.

Trial selection and evaluation

Two of the authors independently reviewed all the titles and abstracts identified in the bibliography searched and excluded the irrelevant trials. The remaining assays were evaluated in full text and disagreements were settled with the participation of the third author.

All three researchers – in accordance with the Cochrane Collaboration guide – independently assessed the validity of the trials selected13. The random sequence generation, the sequence hiding, blinding, information gathering, losses to follow-up during the trial, inclusion of incomplete data, selective outcome reporting, and other biases were all evaluated. Based on this methodology, the risk of biases was classified into high, uncertain, and low.

Data collection

Based on the recommendations from Cochrane Consumers and Communication Review data extraction template14 the analysis of the information extracted was done using an information extraction table. The information that was required but not available after reading the articles was requested to the authors directly. The article with the largest sample was written in Farsi13 and only the abstract was available in English. There were failed attempts to contact the authors in order to obtain the complete data. An investigator extracted the information from the trials, following the table closely. To ensure the accuracy of the data, a second investigator then reviewed the information collected.

Results analyzed

The results analyzed included the average serum potassium in mEq/L during the postoperative period, serum Creatinine in mg/dL three days after surgery, pH immediately after surgery, the volume of infused solution in liters and bicarbonate and chloride in the arterial blood expressed in mEq/L following surgery.

Statistical analysis

This meta-analysis estimated the mean difference with its respective 95% confidence interval (95% CI) for the variables considered, using Review Manager software, version 5.1. An analysis using the fixed or random effects model was completed, based on the existence of statistical heterogeneity. The statistical heterogeneity was evaluated using the Q Cochrane test and the I2 statistic. When I2 was less than 40%, we used the fixed effects model and if I2 was above 40%, the random effects model was used. The sensitivity analysis was completed based on the methodological quality of the trials, removing some trials and re-analyzing the data. Similarly, a sub-group analysis was done, based on the patients’ characteristics and the mode of intervention used.

Results

Trial selection process

The initial search identified 187 articles, of which 182 were ruled out due to failure to meet the eligibility criteria (Fig. 1).

Characteristics of the trials included

Four randomized controlled trials were identified with 237 participants that met the inclusion criteria. All of the trials were double blind. The main characteristics of these trials are shown in Table 1. Lactated Ringer’s was used as the “experimental” intervention, while NSS was used as the “control”; observation times and follow-up after renal transplantation were variable for the various trials, and hence the results of the measurements at similar time intervals were used to make them comparable.

When evaluating the risk of biases in the articles included, we found that most of them used computerized software for randomization. However, the Khajavi et al13 trial is the exception as it fails to indicate how the randomization process was done. All of them used opaque envelopes to hide the allocation and a proper masking method was used in every case. The Modi et al12 trial was classified as “ambiguous risk” due to missing information to rule out any detection, attrition and notification risks. Figs. 2 and 3 illustrate the bias risks.

The results considered for the analysis included the laboratory measurements during the perioperative period that the authors rated as most significant. The potassium difference was not significant at the end of surgery (mean difference (MD): −0.26 mEq/L; 95% CI: −0.58 to 0.05; p = 0.10; I2 = 75%) although it was done through fixed effects; RL resulted in a lower value (Fig. 4).

The secondary results considered show that there is no difference in the Creatinine value expressed in mg/dL on the third postoperative day (MD: −0.05; 95% CI: −0.59 to 0.48; p = 0.85; I2 = 0%) (Fig. 5).

With regard to the acid–base status, the NSS group exhibited higher acidosis, the pH was higher in the LR group (MD:
Literature search:
Databases: Medline (PubMed), Embase, Central Cochrane Database, Lilacs, CINAHL.

Identified

Databases: Medline (PubMed), Embase, Central Cochrane Database, Lilacs, CINAHL.

Excluded because of failure to comply with the protocol criteria (n=182)

Evaluation

Combined search results (n=187)

Excluded – Outcomes excluded from the meta-analysis: (n=1)

Eligibility

Articles evaluated based on eligibility (n=5)

Articles included in the qualitative synthesis (n=4)

Excluded – Outcomes excluded from the meta-analysis: (n=1)

Included

Articles included in the quantitative synthesis (meta-analysis) (n=4)

Fig. 1 – Search flowchart: search results, potentially eligible articles, included and excluded.

Source: Authors.

Discussion

Renal transplant has actually become one additional option for the treatment of chronic renal disease. The 5-year survival is 70%, while the survival for patients that continue on dialysis is only 30%. Patients undergoing renal transplant have multiple comorbidities, including cardiovascular, hypertension, dyslipidemia, hyperphosphatemia and hyperhomocysteinemia, in addition to

Fig. 2 – Risk analysis on meta-analysis biases shown in percentages, considering all the trials included.

Source: Authors.
### Table 1 – Characteristics of the trials selected for the meta-analysis.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Donor type</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Co-interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Malley²</td>
<td>Living or cadaver</td>
<td>51 patients.</td>
<td>LR (n = 25)</td>
<td>Serum Creatinine at day 3 POP</td>
<td>Immunosuppression: steroids, calcineurine and mycophenolate inhibitor or sirolimus.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NSS (n = 26)</td>
<td></td>
<td>Routine radial artery catheter. Central venous catheter discretionary.</td>
</tr>
<tr>
<td>Hadimioglu¹¹</td>
<td>Living</td>
<td>90 patients.</td>
<td>LR (n = 30)</td>
<td>Total daily urinary volume</td>
<td>Immunosuppression: steroids, cyclosporine and mycophenolate. Heparin 5000 IU IV.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NSS (n = 30)</td>
<td>Serum Creatinine at day 3 POP</td>
<td>Radial artery catheter. Central venous catheter.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Plasmalyte (n = 30).</td>
<td>pH, bicarbonate and potassium during the POP.</td>
<td>Maintenance fluids CVP 12–15 mmHg.</td>
</tr>
<tr>
<td>Khajavi³</td>
<td>Living</td>
<td>52 patients.</td>
<td>LR (n = 26)</td>
<td>Serum potassium at the end of surgery</td>
<td>Immunosuppression: steroids, cyclosporine and mycophenolate. Heparin 5000 IU IV.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NSS (n = 26)</td>
<td>pH at the end of surgery.</td>
<td>Use of radial artery catheter. Central venous catheter.</td>
</tr>
<tr>
<td>Modi¹²</td>
<td>Living</td>
<td>74 patients.</td>
<td>LR (n = 37)</td>
<td>Intraoperative and day 1 POP urinary output.</td>
<td>Immunosuppression: methylprednisolone, furosemide and mannitol.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NSS (n = 37).</td>
<td>Serum Creatinine day 1 POP.</td>
<td>Maintain CVP 12 – 15 mmHg. Management of acid–base complications and hydro-electrolytic disorders at the anesthesiologist discretion.</td>
</tr>
</tbody>
</table>

Source: Authors.


pulmonary hypertension²⁴. This represents an anesthetic challenge for the perioperative period²⁵. According to the government data there were 2693 renal transplants in 2008, and 3691 in 2010; this shows a growing number of transplant procedures in the country²⁶,²⁷. General anesthesia is currently the technique of choice; however, regional techniques have proven to be beneficial, particularly in terms of postoperative pain²⁸,²⁹. An in-depth knowledge of the various surgical steps is critical to optimize the surgical conditions³⁰–³².

The use of large volumes of fluids during the intraoperative period has typically reported improved graft function¹⁰,²⁵,³²–³⁹. Fluid therapy is a critical element in the intraoperative management of a patient undergoing renal transplantation⁶⁰,⁶¹, particularly because the multiple physiological and pathological variables increase the complexity of the procedure⁶¹. Classically, the administration of large volumes of potassium solutions, such as LR, may lead to hyperpotassemia and hence NSS¹ has been used instead; several studies indicate that NSS continues to be the choice for this procedure⁴. Recent studies, however, suggest that more balanced approaches, such as LR, may prevent hyperchloremic metabolic acidosis³–⁵, and this is not the case if large NSS volumes are used, as has been shown in other types of patients⁴,⁸,⁴²–⁴⁵.

There is some controversy about the best type of crystalloids to use in a RT patient⁴⁶–⁴⁸. The use of colloids in these patients is limited⁴⁸,³⁴ and it is not recommended because of adverse events, including renal failure⁴⁹–⁵².

This meta-analysis showed that the administration of LR may be an option for fluid management therapy in renal transplantation since contrary to old beliefs, this solution did not elicit higher hyperpotassemia or higher rates of graft dysfunction as shown by the fact that no differences were identified in the Creatinine values three days after surgery. The potassium
When fixed effects were used, LR showed a lower value (Fig. 4). There is significant heterogeneity in the results, such heterogeneity difference was not significant at the end of surgery, though when fixed effects were used, LR showed a lower value (Fig. 4). Further analysis of this variable indicated that although there is significant heterogeneity in the results, such heterogeneity decreases upon removing the Khajavi et al. trial; the explanation could be the difference in renal ischemia time that was longer in the NSS group. The presence of hyperpotassemia in the NSS group could be mainly explained because potassium acts as a buffer in the presence of acidosis. And, as mentioned above, the administration of large volumes of NSS causes hyperchloremic metabolic acidosis. The meta-analysis confirms that the NSS causes metabolic acidosis, probably as a result of hyperchloremia, as illustrated in Figs. 6–8. The patients who received NSS had lower pH values and lower serum bicarbonate, and the data were not heterogeneous for the various trials. Serum chloride was higher in the NSS group, as compared against the patients receiving LR, though there is significant heterogeneity with this particular variable. It should be mentioned however that other anions such as sulfates and phosphates, inter alia, may accumulate in patients with chronic renal disease; nevertheless, crystalloids do not affect the concentration and chloride could be the key factor in the development of metabolic acidosis. To this date, several trials show that hyperchloremia per se could be the cause for an unfavorable outcome in renal function. The success in preventing periorient complications includes proper patient identification and optimization, with an anesthetic plan that integrates the various variables affecting the evolution of the renal transplant. It should be highlighted however, that no

### Table: Postoperative serum potassium levels (mEq/L)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lactato de ringer</th>
<th>SSN</th>
<th>Mean difference</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV, Fixed, 95% CI [mEq/L]</td>
<td></td>
</tr>
<tr>
<td>O’Malley 2005</td>
<td>4.6</td>
<td>0.6</td>
<td>0.8</td>
<td>0.10 [-0.29, 0.49]</td>
</tr>
<tr>
<td>Khajavi 2008</td>
<td>4.8</td>
<td>0.7</td>
<td>0.7</td>
<td>-0.80 [-1.21, -0.39]</td>
</tr>
<tr>
<td>Modi 2012</td>
<td>3.99</td>
<td>0.71</td>
<td>0.59</td>
<td>-0.32 [-0.62, -0.02]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>118</strong></td>
<td></td>
<td><strong>-0.21 [-0.35, -0.07]</strong></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 12.13, df = 3 (P = 0.004); I² = 75%</td>
<td>Test for overall effect: Z = 2.87 (P = 0.007); I² = 75%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table: Serum Creatinine level at day 3 after surgery (mg/dL)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lactato de ringer</th>
<th>SSN</th>
<th>Mean difference</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV, Fixed, 95% CI [mg/dl]</td>
<td></td>
</tr>
<tr>
<td>O’Malley 2005</td>
<td>2.2</td>
<td>1.7</td>
<td>1.8</td>
<td>-0.20 [-1.16, 0.76]</td>
</tr>
<tr>
<td>Khajavi 2008</td>
<td>2.2</td>
<td>2.2</td>
<td>0.7</td>
<td>0.30 [-0.59, 1.19]</td>
</tr>
<tr>
<td>Handimoglu 2008</td>
<td>1.8</td>
<td>1.4</td>
<td>2.2</td>
<td>-0.30 [-1.23, 0.63]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>81</strong></td>
<td></td>
<td><strong>-0.05 [-0.59, -0.48]</strong></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.97, df = 2 (P = 0.62); I² = 0%</td>
<td>Test for overall effect: Z = 0.19 (P = 0.85)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Fig. 3 – Individual analysis of the risk of bias per trial. Source: Authors.

Fig. 4 – Postoperative serum potassium levels (mEq/L). (A) Fixed effect analysis. (B) Random effect analysis. Source: Authors.

Fig. 5 – Serum Creatinine level at day 3 after surgery (mg/dL). Source: Authors.
No adverse effects were described in any of the trials using renal transplantation surgery. The heterogeneity of the trials is that the administration of LR is safe for patients undergoing showed no differences between the two groups. This indicates clinical implications of hyperchloremic metabolic acidosis. Up are needed, in order to obtain a better understanding of the trials with larger numbers of patients and long-term follow-up are needed, in order to obtain a better understanding of the clinical implications of hyperchloremic metabolic acidosis.

The clinically relevant result, Creatinine levels at day 3, showed no differences between the two groups. This indicates that the administration of LR is safe for patients undergoing renal transplantation surgery. The heterogeneity of the trials is low in terms of this variable, making the result even stronger. No adverse effects were described in any of the trials using Lactated Ringer’s therapy, so no conclusions can be made on this particular point.

This meta-analysis exhibits a number of limitations including the small number of trials and a small number of patients, in addition to differences in follow-up times and in the variables evaluated. The observation and follow-up times after renal transplantation varied among the various trials, but the results of the measurements used were from similar time intervals to make them comparable. The outcome that evaluates renal function using 3rd postoperative day Creatinine was only reported in three trials. This limits the interpretation of this variable, because the number of patients is further reduced. The heterogeneity of some of the variables was important; however, it is impossible to avoid heterogeneity in this type of trials, considering the differences in the

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lactato ringer</th>
<th>SSN</th>
<th>Mean difference IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Malley 2005</td>
<td>21</td>
<td>4</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>Handimioglu 2008</td>
<td>21.41</td>
<td>3.7</td>
<td>30</td>
<td>18.2</td>
</tr>
<tr>
<td>Modi 2012</td>
<td>21.62</td>
<td>3.56</td>
<td>37</td>
<td>19.47</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>92</td>
<td>93</td>
<td>100.0%</td>
<td>2.72 [1.74, 3.69]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi²=0.96, df=2 (P=.62); I²=0%
Test for overall effect: Z=5.48 (P<.00001)

Source: Authors.

**Fig. 7 – Post-surgical Arterial blood bicarbonate levels [mEq/L].**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lactato ringer</th>
<th>SSN</th>
<th>Mean difference IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Malley 2005</td>
<td>37</td>
<td>0.07</td>
<td>25</td>
<td>7.37</td>
</tr>
<tr>
<td>Handimioglu 2008</td>
<td>7.42</td>
<td>0.06</td>
<td>30</td>
<td>7.36</td>
</tr>
<tr>
<td>Khajavi 2008</td>
<td>7.34</td>
<td>0.05</td>
<td>26</td>
<td>7.29</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>81</td>
<td>82</td>
<td>100.0%</td>
<td>0.06 [0.05, 0.08]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi²=2.40, df=2 (P=.62); I²=17%
Test for overall effect: Z=6.61 (P<.00001)

Source: Authors.

**Fig. 6 – Postoperative pH.**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lactato ringer</th>
<th>SSN</th>
<th>Mean difference IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Malley 2005</td>
<td>105.7</td>
<td>1.3</td>
<td>30</td>
<td>125.4</td>
</tr>
<tr>
<td>Handimioglu 2008</td>
<td>103.92</td>
<td>1.3</td>
<td>30</td>
<td>125.4</td>
</tr>
<tr>
<td>Modi 2012</td>
<td>106</td>
<td>4</td>
<td>25</td>
<td>111</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>92</td>
<td>93</td>
<td>100.0%</td>
<td>–12.14 [–13.11, –11.18]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi²=212.85, df=2 (P<.00001); I²=99%
Test for overall effect: Z=24.57 (P<.00001)

**Fig. 8 – Post-surgical chloride levels [mEq/L]. (A) Fixed effect analysis. (B) Random effect analysis.**

Source: Authors.
The use of LR in the perioperative period of renal transplant procedures results in similar potassium levels during the postoperative period, higher pH and bicarbonate levels, and lower chloride, with no significant changes on the 3rd day postoperative Creatinine values, despite using a similar infusion volume as compared to NSS.

**Conclusion**

The use of LR in the perioperative period of renal transplant procedures results in similar potassium levels during the postoperative period, higher pH and bicarbonate levels, and lower chloride, with no significant changes on the 3rd day postoperative Creatinine values, despite using a similar infusion volume as compared to NSS.

**Ethical disclosures**

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflict of interests to declare.

**Funding**

The authors did not receive sponsorship to undertake this article.

**REFERENCES**


5. Prough DS, Bidani A. Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology. 1999;90:1247–9.


9. Fournier MS, Bidani A. Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology. 1999;90:1265–70.


