TITLE: Levothyroxine for Solid Organ Donors: A Review of the Clinical-Effectiveness and Guidelines

DATE: 20 May 2009

CONTEXT AND POLICY ISSUES:

Organ transplantation is a life-saving treatment for patients with end-stage cardiac, pulmonary, renal, hepatic, or endocrine failure. Most organs come from donors who die in the intensive care unit after being declared brain dead. Many patients with end-stage organ failure will not get a transplant because the number of indications for transplant and potential recipients have increased, but the number of available organs has not increased sufficiently. In 2001, there were 420 deceased organ donors in Canada, for a rate of 13.5 donors per million population. Seventy-seven per cent of them provided more than one organ or tissue. Currently, more than 4,000 patients are waiting for a transplant. In 2008, 1,803 transplants occurred and 195 persons died while waiting.

During the development of brain death, electrocardiographic, hemodynamic, and histopathological changes occur, with subsequent depletion of circulating hormones and deterioration of organ function. These changes occur in up to 85% of donors and may affect the quality of the donor organ and success of transplant. Aggressive donor management strategies are required to preserve donor organ function. The use of hormonal therapy in potential donors, including thyroxine, corticosteroids, vasopressin and insulin, is one strategy that may improve organ viability and function post-transplantation. There are arguments for using aggressive therapy in hemodynamic unstable donors only (approximately 80% of donors are unstable), or using aggressive therapy in all donors. Studies on the use of thyroxine in hemodynamic stable organ donors have produced conflicting results. One group reports that hypothyroidism has a protective effect against liver damage in rats, and although this data can not be directly applied to humans, it may be possible that the administration of thyroxine could damage human liver tissue during harvesting.
A United Network for Organ Sharing (UNOS) retrospective cohort study using consecutive records of 10,292 brain-dead donors provides evidence that triple hormone therapy has benefit (i.e., improved one-month survival and lower early graft dysfunction) with minimal risk compared to not using triple therapy. The Canadian guidelines on organ donor management endorse the use of combined hormonal therapy which includes, in adults: tetraiodothyronine (levothyroxine; L-thyroxine; T₄) 20 µg intravenous bolus followed by 10 µg/hour by intravenous infusion; vasopressin 1 unit intravenous bolus followed by 2.4 units/hour by intravenous infusion; and methylprednisolone 15 mg/kg (≤1 g) intravenously every 24 hours. Yet, the same guidelines identify gaps in research: 1) There is a need to study orally and intravenously administered T₄ and tri-iodothyronine (T₃) in humans to determine the kinetics, biological effects, optimum dosing, peripheral conversion times, and effect of corticosteroids; 2) There is a need for studies to determine whether or not combined hormonal therapy improves hemodynamics, organ function, and organ utilization.

This report reviews the evidence for the use of levothyroxine in combination with vasopressin and methylprednisolone administered to solid organ donors: whether or not the combined hormonal therapy improves graft survival in the recipient; whether or not similar outcomes are obtained if levothyroxine is not used; and whether or not levothyroxine should be given as a bolus or as an infusion.

RESEARCH QUESTIONS:

1. What are the clinical benefits and harms of levothyroxine used in combination with vasopressin and methylprednisolone administered to solid organ donors to increase the number of viable organs?

2. What are the guidelines for dosing and administering levothyroxine when used in combination with vasopressin and methylprednisolone in solid organ donors?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 2, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and April 2009. No filters were applied to limit the retrieval by study type. Internet links were provided, where available.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, controlled clinical trials, observational studies, and evidence-based guidelines.

SUMMARY OF FINDINGS:

There were no health technology assessments, systematic reviews, or meta-analyses identified on the clinical benefits and harm of levothyroxine used in combination with vasopressin and methylprednisolone.
Randomized controlled trials

No randomized controlled trials (RCT) were identified. However, a randomized, double-blind, placebo controlled phase 1/phase 2 trial is underway at the London Health Sciences Centre in London, Ontario to determine the efficacy and pharmacokinetics of oral thyroid therapy in organ donors. ¹⁰ Specifically, this trial compares the pharmacokinetics and the reversibility of hemodynamic instability in organ donors of oral versus intravenous administration of thyroid hormone (T₃ and T₄). The primary outcome is the percentage of time patients require inotropic support prior to organ procurement. Secondary outcomes include the pharmacokinetic profiles of oral versus intravenous T₃ and T₄, the number of organs donated, and thyroid function at time of brain death.

Observational studies

Three retrospective cohort studies were retrieved and study details can be found in Appendix 1.

Van Bakel et al. reviewed 119 consecutive donor records.¹¹ The donors were divided into three groups: a hormonal group receiving thyroxine (T₄), methylprednisolone, dextrose and insulin, a steroid group receiving methylprednisolone only, and a control group without hormonal or corticosteroid therapies. There was no statistical difference between the three groups for vasopressin use, for pulmonary capillary wedge pressure, and for the number of organs procured. Both the hormonal group and the steroid groups required less α- and β-adrenergic support (i.e., dopamine, phenylephrine, dobutamine etc.) compared to the control group, but only the hormonal group reached statistical significance (see Appendix 1). Adrenergic agents are required to support blood pressure; however in high doses, they can cause injuries to organs intended for transplantation. The authors concluded that a reduction in adrenergic use confirms the hemodynamic benefits of hormonal therapy.

Two studies were conducted by Salim et al.⁵,¹² using database records. One study evaluated aggressive donor management (ADM) as a strategy to decrease the number of donors lost due to cardiovascular collapse (CVC).¹² The ADM protocol consisted of: 1) early identification of potential donors; 2) ICU admission with management by a dedicated team; and 3) early and aggressive resuscitation with fluids, vasopressors (agents not specified), and hormonal therapy (1 ampoule of 50% dextrose, 2 g methylprednisolone, 20 units of regular insulin, and 20 µg of levothyroxine followed by an intravenous infusion of 10 µg/h) before the declaration of brain death and before consent for donation. Three groups were compared: one centre that began using the ADM protocol in 1999 (LAC-post, n=341); the same centre before it began using the ADM protocol between 1995 and 1998 (LAC-pre, n=694); and eight other centres that served as the control group (Centre A, n=2,915). Results are reported in Appendix 1. The incidence of CVC per potential donor was statistically significantly less in the group after ADM was instituted compared to the group before ADM and compared to the control group. Similarly, more organs were harvested per potential donors with the ADM protocol. The number of organs recovered per actual donor was less with ADM compared to the other two groups, but it was not reported if this was statistically significant. Salim et al. used ANOVA to test for overall differences between the three groups, but the overall p value was not reported. In the methods section of their report, it was unclear what type of post-hoc test was used. It would appear that Student’s t-test was used for pairwise comparisons.

Using the records of patients who donated organs, the same authors compared patients who received levothyroxine (T₄) to those who did not.⁵ Of 123 patients, 96 (78%) received T₄. This group required vasopressor therapy (indicating a more hemodynamically unstable population)
whereas donors that did not get T₄ had no or minimal vasopressor requirement. The T₄ group had significantly more organs procured per donor compared to the group that did not get T₄. A sub-group analysis of donors who died with traumatic head injuries revealed no differences in the number of organs donated per patient when comparing those who received T₄ and those who did not. Conversely, in the group with non-traumatic head injuries, there was a statistical difference in favor of the T₄ group for the number of organs donated compared to the group who did not receive T₄. There was no difference in the type of organ recovered or in brain-death associated complications with or without T₄. The authors concluded that the addition of T₄ in hemodynamically unstable donors yielded significantly more organs donated per patient compared with a group of hemodynamically stable donors.

Limitations

No high quality evidence from health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials was indentified. The statistical significance reported in one observational study is invalid because of the use of erroneous statistical methods and should not be considered. A student’s t-test was used to compare the three groups, which is inappropriate. The other two cohort studies had sample sizes of 119 patients and 123 and were based on retrospective records obtained between 2000 and 2005. Cohort studies may be subject to selection bias. The studies did not account for potential confounders. This review is limited in that it only considered studies published since 2004 and in English.

Guidelines on dosage and dosage form

Regarding dosage, no studies were found that evaluated the optimal dosing regimen of levothyroxine when used in combination with methylprednisolone and vasopressin.

Regarding the route of administration, no studies on the stability of levothyroxine sodium in intravenous solutions were retrieved. In Canada, levothyroxine sodium is indicated for thyroid replacement or supplemental therapy in patients suffering from hypothyroidism. It is available in a tablet form for oral use (Synthroid®, Eltroxin®) and in a powder form for intravenous or intramuscular injection (Levothyroxine Sodium for Injection). The powder form contains special buffers that permits reconstitution with 5 mL of normal saline. Once reconstituted, stability tests have shown that levothyroxine is stable for up to 48 hours, if retained in its original vial. Otherwise, levothyroxine is hydrophobic and adsorbs to glass and plastic containers and tubings. The extent of adsorption is not known but is believed to be significant. Furthermore, it is poorly soluble at the pH of many intravenous solutions and undergoes rapid degradation in aqueous solutions. Storage of such solutions is not recommended for more than two hours, after which significant loss of potency occurs. The administration of levothyroxine as an intravenous piggyback is not recommended.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The studies identified focused on the organ donors. They did not consider clinical outcomes in the transplanted patients such as improved graft survival in the short- and long-term. One retrospective cohort study showed no difference in the number of organs procured between a donor group receiving combination hormonal therapy, a steroid group, and a control group. Another retrospective cohort study showed a statistically significant increase in the number of organs donated with the use of levothyroxine. One on-going RCT will determine the efficacy and pharmacokinetics of thyroid replacement therapy in organ donors. Whether or not levothyroxine is stable in mini-bags and can be administered as an infusion has not been studied. Similarly,
no information was identified on what constitutes the optimal dosing regimen of levothyroxine combined with methylprednisolone and vasopressin. Considerations for decision-making about use of levothyroxine for solid organ donors include the lack of high-quality evidence from systematic reviews or randomized controlled trials, and the paucity of information on clinical benefit and harms to the donor or recipient.

PREPARED BY:
Christine Perras, BSc Phm MPH, Research Officer
Michelle Clark, BSc, Research Assistant
Emmanuel Nkansah, BEng, MLS, MA, Information Specialist

Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
REFERENCES:


*Levothyroxine for Solid Organ Donors*

Appendix 1: Summary of Retrospective Cohort Studies on the Clinical-Effectiveness of Levothyroxine in Solid Organ Donors

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Bakel 2004</td>
<td>n=119</td>
<td>control group</td>
<td>vasopressin use</td>
<td>no statistical differences between the 3 groups for vasopressin use (p=0.58)</td>
</tr>
<tr>
<td></td>
<td>consecutive donor records</td>
<td>no hormonal therapy or corticosteroids vs.</td>
<td>pulmonary capillary wedge pressure (PCWP)</td>
<td>no statistical differences between the 3 groups in PCWP at any time point (p=0.945)</td>
</tr>
<tr>
<td></td>
<td>July 2000 to October 2001 (15 months)</td>
<td>steroid group</td>
<td>α- and β-adrenergic support (dopamine, phenylephrine, or combination of various agents)</td>
<td>greater decrease in the use of adrenergic support in the combination group compared to the control group (p=0.02 for α-adrenergic drugs and p=0.002 for β-adrenergic drugs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>combination group</td>
<td>number of organs procured</td>
<td>no difference in the number of organs procured between the 3 groups (p=0.6)</td>
</tr>
</tbody>
</table>
### Study Design

**Methodology:**
- Salim 2006
- Database records from the Southern California regional organ procurement organization of patients admitted to Level 1 trauma teaching centres (1995 to 2003)

### Interventions

**Aggressive Donor Management (ADM):**
- Early identification of potential donors
- ICU admission with management by a dedicated team
- Early and aggressive resuscitation with fluids, vasopressors, and hormone therapy
  - 1 ampoule of 50% dextrose, 2 g methylprednisolone, 20 units of regular insulin, and 20 µg of levothyroxine then 10 µg/h IV before consent for donation (n=1 centre using data from 1999 to 2003 and referred to as LAC-post)

**No ADM:**
- Includes 8 centres referred to as Centre A and 1 centre using data from 1995 to 1998 referred to as LAC-pre

### Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LAC-pre</th>
<th>Centre A</th>
<th>LAC-post</th>
</tr>
</thead>
<tbody>
<tr>
<td># referrals for donation</td>
<td>341</td>
<td>694</td>
<td>2,915</td>
</tr>
<tr>
<td>Incidence of cardiovascular collapse (CVC)</td>
<td>19.63%, p&lt;0.001</td>
<td>8.67%, p&lt;0.0001</td>
<td>1.60%</td>
</tr>
<tr>
<td>Conversion rates</td>
<td>26.6%</td>
<td>41.2%</td>
<td>41.4% (statistical significance not reported)</td>
</tr>
<tr>
<td>Number of organs harvested per potential donor</td>
<td>2.07, p=0.02</td>
<td>2.09, p&lt;0.01</td>
<td>2.41</td>
</tr>
<tr>
<td>Number of organs recovered per actual donor</td>
<td>3.81</td>
<td>3.89</td>
<td>3.55 (statistical significance not reported)</td>
</tr>
</tbody>
</table>

### Results

- **CAUTION:** Please consider absolute numbers only and not statistical significance.
<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salim 2007⁵</td>
<td>n=123</td>
<td>all patients received ADM* with or without T₄</td>
<td>T₄ use</td>
<td>T₄ used in 78% (n=96) of donors</td>
</tr>
<tr>
<td></td>
<td>records of patients who successfully donated organs</td>
<td>number of organs donated per donor</td>
<td>T₄ group: 3.9±1.7, no T₄ group: 3.2±1.7, p=0.048</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sub-group analysis: trauma (n=97) vs. no trauma patients</td>
<td>type of organ donated</td>
<td>trauma: no difference between T₄ group vs. no T₄ group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2001 to 2005</td>
<td>brain-death associated complications</td>
<td>non-trauma: T₄ group: 3.0±1.7, no T₄ group: 1.7±1.3, p=0.052</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>no difference in the type of organ recovered except for pancreas: T₄ group: 46%, no T₄ group: 5%, p=0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>no difference between those with or without T₄ in either the trauma and non-trauma groups</td>
<td></td>
</tr>
</tbody>
</table>

* ADM included pulmonary artery catheterization; aggressive IV fluid resuscitation; vasopressor infusion for mean arterial pressure <70 mmHg; hormonal therapy was used when the combined vasopressor need exceeded 10 µg/kg/min of epinephrine, dopamine, or their combination; hormonal therapy consisted of one ampoule of 50% dextrose, 2 g methylprednisolone, 20 units of regular insulin, and 20 µg of levothyroxine sodium (T₄) followed by 10 µg/h IV infusion⁵
ADM=aggressive donor management; ICU=intensive care unit; IV=intravenous