The Canadian Radiological Foundation

Fondation radiologique canadienne

A double blind, randomized controlled trial examining the efficacy of the use of tissue plasminogen activator (tPA) in intra-abdominal collections in children – a prospective study

Status:

- ✓ Health Canada Approval
- ✓ Institutional Research Ethics Board Approval

Planned start date: April 2012

Background

Abdominal abscesses are common in childhood, resulting usually from perforated appendicitis, but also from other pathologies. Intra-abdominal abscesses are painful, potentially dangerous lesions presenting with focal tenderness, spiking fever, prolonged ileus, leukocytosis and bacteremia. Untreated, abdominal abscesses may progress to full-blown life threatening sepsis.

Historically, abscesses were treated with surgical drainage and washout. Percutaneous drainage using imaging guidance has now become the first line therapy, providing an effective minimally invasive alternative to surgery. Drainage may be less effective if the fluid is thick or the abscess septated. Instillation of tissue plasminogen activator (tPA) into an abscess cavity facilitates drainage by breaking down septations. Institutions worldwide, including Sick Kids, facilitate abscess drainage using intracavitary tPA. However it is "off label", the timing of administration or dose is not standardized, and the decision to use is frequently late, based on the pus viscosity, resistance to drainage, and septations on ultrasound. Previous studies support the safety of tPA use in abscesses.

Purpose

To establish the efficacy of tPA (once-per-day) in the treatment of pediatric intra-abdominal abscesses (study intervention group) and compare it to our standard clinical practice of saline flushes (control group).

1) Primary Objective:

   To determine whether there is a difference in the length of drainage catheter indwelling time (in hours), between the study intervention group and the control group.

Hypothesis: Administration of tPA throughout the dwell period of the drainage catheter will significantly reduce the time that the catheter remains in-situ.

2) Secondary Objectives:

#1 - To determine whether there is a difference in the duration of hospital stay (in hours) between the study intervention group and the control group.

Hypothesis: Administration of intracavitary tPA throughout the dwell period of the drainage catheter will significantly reduce the length of hospital stay.

#2 – To determine whether there is a difference in the rate of complete abscess resolution in the study intervention group compared to the control group.

Hypothesis: The rate of complete resolution of the abscess will be faster in those patients treated with tPA than those treated with saline.

#3 – To determine whether there is a difference in the time taken (in days) for the patient's clinical and laboratory markers to normalize in the study intervention group compared to the control group.

Hypothesis: Facilitation of abscess drainage with tPA will lead to faster resolution of these markers in the study intervention group compared to the control group

#4 – To document adverse events related to the use of tPA in pediatric intra-abdominal abscesses.

Hypothesis: When at-risk patients (list specified) are excluded from the study, use of tPA in intra-abdominal abscesses does not directly cause significant complications.

Design and Methods

A prospective, double-blind, randomized, controlled trial. "Double-blind" refers to blinding of the patients, parents, and attending clinicians (surgeons and interventional radiologists). Random sequence generation will be performed by the research support pharmacist, who will allocate patients into either the study intervention group to receive daily tPA, or the control group to receive normal saline, on identical regimens.

Based on 'best practice" consensus, 2mg tPA in 4mls saline per abscess was chosen as the dose of tPA . The study intervention group will have each drainage catheter (maximum 3 drains/patient) flushed 3 times/day: once with tPA (2mg in 4mls + 1ml saline) and twice with 5mls sterile normal saline. The control group follows standard care: each drainage catheter flushed 3 times/day, once with saline (4mls + 1 ml sterile saline) and twice with 5mls normal saline.

Data collection will include:

1) Clinical parameters (daily maximum temperature, heart rate, 24 hour catheter drainage volume);

2) Laboratory parameters (pre- and Day 3 post-procedure)

3) Ultrasound (pre- and post-drainage).

Patients complete the study when their drains are removed. Removal of the drainage catheter(s) will be decided by consultation amongst the clinical team (interventional radiologist, surgeon), based on:

1) Patient's clinical improvement - defined as resolution of at least 2 of 3 features:

    i) Fever – normal defined as < 37.4°C orally.

    ii) Tachycardia - according to age-specific normal ranges employed at SickKids.

    iii) White cell count –according to age-specific normal ranges employed at SickKids.

2) A reduction in fluid drainage over the previous 24hrs to <10ml.

3) Resolution of the collection upon imaging - "resolution" defined as one axis measuring <2.0cm (collections often resolve into flat, discoid lesions).

Statistical Analysis

Descriptive statistics (means, medians, proportions, standard deviations), comparative statistics (t-tests, Chi-square tests) and non-parametric statistics where appropriate will be used.

The primary analysis will be a 2 sample t-test with maximum length of drain time (hours) as the primary outcome. It is not expected that other variables will confound the group-outcome association; however baseline characteristics between groups will be compared. In small sample sizes randomization may not completely adjust imbalances in variables. Multiple regressions will adjust for these variables (e.g. drain size, number of abscesses).

The minimal clinically significant difference between groups is 1.5 days. Estimates of drain time were 3±1.5 days in the tPA group and 4.5±2 days in controls. Required sample size to detect this difference (81% power at the 5% level of significance) is 23/group. A small adjustment for potential correlation (< 10%) of independent factors increases this sample size to 25/group.

Impact

Lengthy hospital stays are associated with increased risks of nosocomial complications, repeated imaging and bloodwork, burdening the patients and the healthcare system. Prolonged abscesses (+/-sepsis) significantly increases risks of co-morbidities and complications (e.g. sepsis, ileus, hospital-acquired pneumonias etc). The time and financial burden to a family is considerable. Initiatives reducing risks and costs to the patient, health service, and society warrant investigation.

This study may show significant patient benefits from shorter drainage times, faster clinical resolution, and significantly shorter hospital stay.