Study Protocol V6 for:

Negative Pressure Wound Therapy versus Alternate Temporary Abdominal Closure Methods for Critically Ill Adults with Open Abdominal Wounds: A Systematic Review

Derek J. Roberts, MD, David A. Zygun, MD, MSc, FRCPC, Jan Grendar, MD, Chad G. Ball, MD, MSc, FRCSC, Helen Lee Robertson, MLIS, Jean-Francois Ouellet, MD, FRCSC, Andrew W. Kirkpatrick, MD, MHSc, FRCSC, FACS

From the Departments of Surgery (Drs. Roberts, Grendar, Ball, Ouellet, and Kirkpatrick), Community Health Sciences (Drs. Roberts and Zygun), Critical Care Medicine (Drs. Roberts, Zygun, and Kirkpatrick), and Clinical Neurosciences (Dr. Zygun) and the Regional Trauma Program (Drs. Ball, Ouellet, and Kirkpatrick) and Health Sciences Library (Ms. Robertson), University of Calgary and the Foothills Medical Centre, Calgary, Alberta, Canada

Contact Persons:

Derek J. Roberts, MD
Departments of Surgery, Community Health Sciences, and Critical Care Medicine
University of Calgary
ICU Administration, Ground Floor McCaig Tower
Foothills Medical Center
3134 Hospital Drive Northwest
Calgary, Alberta
Canada
T2N 5A1
Tel.: 403-944-0747
Fax: 403-283-9994
E-mail: Derek.Roberts@Dal.Ca

Andrew W. Kirkpatrick, MD, MHSc, FRCSC, FACS
Professor, Departments of Surgery and Critical Care Medicine
University of Calgary
1403-29th Street Northwest
Calgary, Alberta
Canada
T2N 2T9
Tel.: 403-944-1443
Fax: 403-944-8799
E-mail: Andrew.Kirkpatrick@AlbertaHealthServices.Ca

1. Background, Rationale, and Objectives:

Open abdominal management with temporary abdominal closure (TAC) is increasingly utilized in critically ill trauma, general, and vascular surgery patients.[1] Common indications for leaving the abdomen open include damage control laparotomy, intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS), planned re-laparotomy, and the inability to achieve postoperative fascial closure.[1-3] A number of different TAC techniques and/or devices have been utilized, ranging from simple skin approximation to the Bogotá bag, absorbable mesh, Wittmann patch™ (Starsurgical Inc., Burlington, WI), Barker's vacuum pack technique, and commercial negative pressure wound therapy (NPWT), among others.[1-3]

While NPWT is favoured over other TAC methods by some given the technique's various purported benefits, others have reported concerns over associations with recurrent ACS and increased intestinal and enteroatmospheric fistulae.[4-7] NPWT appears to more effectively remove pro-inflammatory cytokine-rich peritoneal fluid than alternate methods of TAC, which may reduce the systemic inflammatory response and associated organ dysfunction.[8,9] It also prevents visceral adherence to the abdominal wall while maintaining medial fascial traction, which may enhance subsequent fascial closure rates.[10,11]

Although a previous systematic review afforded a weighted pooled outcomes analysis of NPWT-associated fascial closure and mortality, this investigation's findings were limited by its exclusive inclusion of uncontrolled case series.[12] Since then, the results of several randomized and observational studies examining the differential efficacy of NPWT versus alternate TAC methods have been reported.[8,11,13-21] Thus, we will conduct a systematic review of published and unpublished studies to determine the comparative efficacy of NPWT versus alternate TAC methods on mortality, length of hospital or intensive care unit (ICU) stay, fascial closure rate, and adverse events in critically ill adults with open abdominal wounds.

2. Structured Clinical Question:

In adult ICU patients requiring open abdominal management, does use of NPWT result in an improved in-hospital mortality, fascial closure rate, and length of hospital or ICU stay as compared to alternate TAC techniques?

2.1 PICOD Components:

P: Adult (≥ 16-years-old) ICU patients requiring management of type II (exposed bowel or omentum) or III (presence of intra-abdominal sepsis) open abdominal wounds[22] due to trauma, intra-abdominal sepsis, IAH/ACS, or vascular surgical emergencies

I: NPWT, including the ABThera™ open abdomen NPWT system [Kinetic Concepts Inc. (KCI), San Antonia, TX] and the KCI vacuum-assisted closure (VAC) device

C: An alternate NPWT technique or TAC method (e.g., skin approximation, Bogotá bag, absorbable mesh, Wittmann patch™, or Barker's vacuum pack technique,[2,23,24] among others)

O: In-hospital mortality, fascial closure rate, and length of hospital or ICU stay, and other outcomes (see below)

D: Comparative studies (i.e., RCTs, cohort studies, and case-control studies)

3. Outcomes:

3.1 Primary Outcome:

The primary outcome will be in-hospital mortality (i.e., mortality at or before hospital discharge).

3.2 Secondary Outcomes:

Secondary outcomes will include duration of hospital or ICU stay, fascial closure rate, effect on intra-abdominal pressure (IAP), ACS occurrence rate (defined as sustained IAP > 20 mmHg associated with new organ dysfunction/failure[25]), and frequency of abdominal fistula formation or infectious complications (e.g., intra-abdominal abscesses or surgical site infection).

4. Protocol:

Methods for inclusion and analysis of articles and reporting of study results will occur according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses[26] and the Meta-analysis of Observational Studies in Epidemiology proposal.[27]

5. Search Strategy:

Two surgical-investigators (D.J.R., A.W.K.) will create the preliminary search strategy. A medical librarian (H.L.R.) will subsequently refine this strategy by conducting iterative database queries and incorporating novel terms when new potentially relevant citations are found. Searches will be conducted in the following databases from their first available date without language restrictions: MEDLINE, PubMed, EMBASE, Scopus, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the NHS Economic Evaluation Database, the Health Technology Assessment Database, and the Turning Research into Practice (TRIP) database. To identify unpublished studies, we will also investigate two clinical trials registries (ClinicalTrials.gov and Current Controlled Trials), question field experts, and write the manufacturer of a commercial NPWT device (KCI, San Antonio, TX). Additional citations will be located using the PubMed "related articles" feature and hand-searching reference lists of included trials and relevant reviews[12,28,29] and guidelines.[1-3] We will write study authors for additional information as necessary.

For our MEDLINE search, we will construct search filters for the themes IAH/ACS, NPWT and alternate TAC methods, trauma or sepsis, and critical care using a combination of exploded Medical Subject Heading (MeSH) terms and text words, each combined through use of the Boolean operator "OR." The below search themes will subsequently be combined with use of the Boolean operator "AND" in varying combinations (similar searches will be conducted in remaining databases):

1. The IAH/ACS search theme will contain the key words "abdominal pressure," "intra-abdominal pressure*," "intraabdominal pressure," "intra-abdominal hypertension," "intraabdominal hypertension," "intra-vesicular pressure,"

"intravesicular pressure," "bladder pressure*," OR "abdominal compartment syndrome*"

2. The NPWT and alternate TAC methods search theme will contain the MeSH terms "Abdominal Cavity/su [Surgery]," "Abdominal Wall/su [Surgery]," "Laparotomy," "Decompression, Surgical," "Negative Pressure Wound Therapy," OR "Vacuum" as well as the key words "decompressive laparotomy," "decompressive celiotomy," "laparostomy," "laparostomies," "vacuum-assisted closure," "topical negative pressure wound therapy," "VAC," "vacuum pack," "Bogotá bag," "towel clip," "temporary silo," OR "Wittmann patch"
3. The trauma or sepsis search theme will contain the MeSH terms "Sepsis," "Peritonitis," OR "Abdominal Injuries" as well as the key words "intra-abdominal sepsis" OR "intraabdominal sepsis"
4. The critical care search theme will contain the MeSH terms "Critical Care," "Intensive Care," "Intensive Care Units," "Critical Illness," OR "Postoperative Care."

6. Study Selection:

Two reviewers (D.J.R., J.G.) will independently screen titles and abstracts, review potentially relevant citations in full, and decide on study inclusion. We will use the following inclusion criteria: 1) design was a comparative trial; 2) study participants were adult (≥ 16-years-old) ICU patients requiring management of type II (exposed bowel or omentum) or III (presence of intra-abdominal sepsis) open abdominal wounds[22] due to trauma, intra-abdominal sepsis, IAH/ACS, or vascular surgical emergencies; 3) intervention included NPWT; 4) comparison was an alternate NPWT technique or TAC method [e.g., skin approximation, Bogotá bag, absorbable mesh, Wittmann patch™ (Starsurgical Inc., Burlington, WI), or Barker's vacuum pack technique,[2,23,24] among others]; and 5) the study reported either mortality or fascial closure as an outcome. We will use the definitions afforded by Boele van Hensbroek and colleagues[12] for methods of TAC and exclude studies without a comparison group and those that employed the Barker's vacuum pack technique only. No language restrictions will be imposed.

In accordance with present recommendations on systematic reviews and meta-analyses,[30,31] and because previous investigations have shown that many NPWT and surgical device trials are terminated early (increasing potential for publication bias),[28] we will include abstract and unpublished investigations. French or German-speaking co-investigators or other colleagues will translate non-English-language abstracts of interest and included articles. Eligibility disagreements will be resolved by consensus or arbitration (A.W.K.).

7. Data Extraction and Methodological Quality Assessment:

The same two reviewers will extract data on: 1) trial design; 2) study participant characteristics, including age, indication for open abdominal management, wound classification,[22] initial systolic blood pressure (SBP) and illness severity [including injury severity score (ISS) and/or Acute Physiology and Chronic Health Evaluation-II (APACHE-II)[32]], presenting acid/base status (arterial pH, base deficit, and serum lactate), international normalized ratio (INR), and body temperature after presentation as well as

amount of fluid (blood product and crystalloid) resuscitation in the first 24-hours; 3) TAC technique; and 4) outcome measures (described above).

Two reviewers with methodologic expertise (D.J.R., D.A.Z.) will evaluate risk of bias. Randomized controlled trials (RCTs) will be graded with the five-point Jadad score, which includes four questions on randomization and blinding and one on withdrawals and dropouts[33] and the Cochrane Collaboration criteria.[34] Cohort studies will be assessed using the Newcastle-Ottawa scale.[35] This nine-point scale evaluates selection and attrition bias, inter-group comparability, and ascertainment of exposure bias using a starring system. As one item on this scale is irrelevant ("demonstration that outcome of interest was not present at start of study"),[36] the maximum score for cohort studies will be eight rather than nine. Studies will also be appraised for sources of "other bias" (as described by the Cochrane Collaboration[34]) that could affect mortality or fascial closure rates independent of NPWT. We will define theses sources as inadequate descriptions of (or significant differences in) initial systolic blood pressure (SBP), illness severity scores, patient physiology (acid/base status, INR, or body temperature), and amount of fluid resuscitation.[37]

8. Analysis:

We will standardize dichotomous study outcomes using the relative risk as the chosen summary measure of association (with associated 95% confidence intervals). Whenever possible, outcomes will be re-calculated using an intention-to-treat, rather than per-protocol, method of analysis. Although it is anticipated that the clinical heterogeneity of studies will preclude formal outcome pooling, if possible meta-analysis of included studies will be performed using Stata version 12.0 (Stata Corp., TX). Statistical heterogeneity will be assessed using the I^2 statistic (with a value greater than 50% indicating at least moderate heterogeneity) and Q test (with a p value < 0.05 indicative of significant heterogeneity).

In order to produce a pooled relative risk, we will use a random-effects model. Fixed effects models will also be analyzed to ensure robustness of the model chosen and susceptibility to outliers. Results will be represented graphically using forest plots with one plot for each study outcome of interest with data available.

Again, if possible, we will assess publication bias on similarly designed studies that utilized comparable NPWT and alternate TAC methods through visual inspection of the Forest plot and Begg's and Egger's tests.

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