Appendix 1 (as supplied by the authors): SPIRIT Study Protocol

Original Title
Hyoscine butylbromide versus acetaminophen for acute abdominal pain in children: a randomized controlled trial

Clinicaltrials.gov Identified Number: NCT02582307

Sponsor
Dr. Naveen Poonai

Qualified Principal Investigator
Dr. Naveen Poonai

Co-Investigators (Name and Department):
Samina Ali MDCM, Paediatrics, University of Alberta
Rod Lim, MD Paediatrics, Western University
Kamary Coriolano PhD, Children's Hospital, LHSC
Andreana Butter MD, Surgery, Western University
Michael Miller PhD, Children's Hospital, LHSC
Dhandapani Ashok MD, Paediatrics, Western University
Gary Joubert, MD Paediatrics, Western University
Graham Thompson MD, Paediatrics, University of Alberta
Sharlene Elsie, Paediatrics, Western University
Kriti Kumar BSc, Paediatrics, Western University
Shaily Brahmbhatt BSc, Paediatrics, Western University
Emily Dzongowski BSc, Paediatrics, Western University
Holly Stevens BSc, Paediatrics, Western University
Priti Gupta BSc, Paediatrics, Western University

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Statement of Compliance

The trial was conducted in accordance with Good Clinical Practice (GCP) as described in Health Canada's section C.05.010/Division 5 of the Food and Drugs Regulations, International Conference on Harmonization-Good Clinical Practice (ICH-GCP E6 R2), Tri-Counsel Policy Statement (TCPS2, 2014); applicable federal, provincial and local regulatory and legislative requirements. The Qualified and Participating Site Investigator(s) assured that no deviation from, or changes to the protocol took place without prior documented authorization (no objection letter - NOL) from Health Canada (Therapeutic Products Directorate) and documented approval from a duly constituted Research Ethics Board (REB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study completed Human Subjects Protection and ICH-GCP Training. The protocol, informed consent form(s), recruitment materials, and all participant materials were submitted to the REB for review and approval. Approval of both the protocol and the consent form were obtained before any participant was enrolled. Any amendment to the protocol required review and approval by the REB before the changes were implemented to the study as well as authorization from Health Canada. All changes to the consent form were REB approved.

Roles and responsibilities

The main sponsor was also the principal investigator who conducted the study with support of all collaborators listed below. Funders did not have any direct role as a decision maker. This was a single center trial therefore, there was no summary of roles and responsibilities from other centres.

Team Member	Project Responsibilities
Naveen Poonai	Qualified Investigator who was responsible for all aspects of study design, oversight of trial logistics at all sites, supervision of data management. He managed monthly teleconference meetings to provided updates, resolved issues, and obtained feedback. He reviewed protocol deviations and violations.
Kamary Coriolano	He served as the Clinical Project Manager and was responsible for coordinating and managing the trial including day to day operations. He provided support on protocol development, Health Canada applications, REB applications, recruitment, and data management.
Samina Ali	She served as a content expert with respect to valid assessment of paediatric pain and ensured that the design of the trial was methodologically rigorous and clinically relevant, patient-oriented outcomes are captured for effective knowledge translation.
Andreana Butter	She served as a content expert to define organic etiologies for abdominal pain and critically reviewed the manuscript for important intellectual content.
Graham Thompson	He served as a content expert for valid assessment of paediatric pain and ensure the design of the trial is methodologically rigorous and clinically relevant. He also helped ensure that patient-oriented outcomes are captured for effective knowledge translation. He critically reviewed the manuscript for important intellectual content.
Michael Miller	He developed the statistical analysis plan and carried out the statistical analysis.
Dhandapani Ashok	He critically reviewed the manuscript for important intellectual content and served as a content expert for non-specific and functional abdominal pain.
Rod Lim	As the administrative lead of the ED, he took responsibility for oversight and operations of the trial during absence of the principal investigator. He critically reviewed the manuscript for important intellectual content.

Gary Joubert	He assisted in conceptualization and design of the study as a knowledge user.
Kriti Kumar and Shaily Brahmbhatt	They worked with the statisician to create the data collection instrument and convert it into a REDCap data project and maintained its upkeep.
Priti Gupta and Holly Stevens	They helped facilitate the patient engagement focus group and translated those findings into recommendations for the study protocol.
Sharlene Elsie and Emily Dzongkowski	They assisted with data collection, verification and cleaning of the data and creation of the Excel spreadsheet for statistical analysis.

Deviations from Registered Protocol

(i) We used only the VAS to determine eligibility and assess pain because it has established reliability using a tablet device (1) and we believed it was more acceptable to the age range under study compared to the Faces Pain Scale – Revised (2).

(ii) We used Southwestern Ontario's electronic medical record (EMR) to identify recidivism in participants unable to be contacted by phone. The system provides access to all medical records across Southwestern Ontario, Kitchener-Waterloo, and the Niagara Peninsula.

(iii) We added several exclusion criteria (see below) prior to commencing enrollment.

The first two amendments were made after the first patient was enrolled and the third amendment was made after three patients were enrolled.

Background and Rationale

Deferred

Objectives

1) To determine the analgesic efficacy of single-dose oral HBB in comparison to acetaminophen in children with acute abdominal pain

2) To compare the time to resolution of abdominal pain between the two agents

3) To compare the incidence of adverse effects between the two agents

4) To compare caregiver satisfaction between groups

5) To compare length of stay between groups.

Trial Design

Randomized, blinded, double-dummy, two-arm, parallel-group, superiority trial

Hypothesis

Hyoscine butylbromide or Buscopan (HBB) is superior to acetaminophen for children with non-specific, colicky abdominal pain

Setting

Pediatric emergency department (ED) of London Health Sciences Center, London, Ontario

Recruitment

Potential participants were pre-screened using the EMR by a research assistant (RA) consecutively during their hours of availability (1700 - 2300 hours per day, 7 days per week). Patients who were within the specified age range and had a triage complaint of abdominal pain were identified by the RA. At this point, the RA notified the treating physician of a potential participant. The RA completed the screening process in person after treating physician's clinical assessment and diagnostic workup (if any) was complete and after obtaining permission from the treating physician to do so. The RA then confirmed eligibility with the treating physician and obtained written informed consent.

Inclusion Criteria

(i) Children 8-17 years

(ii) Presenting to the ED with acute or chronic colicky abdominal self-reported as “crampy”, “coming in waves”, or “squeezing”

(iii) Rated ≥ 40 mm on a 100 mm visual analog scale (VAS) (3) immediately prior to enrollment

NB. We included patients with vomiting or diarrhea if pain persisted despite antiemetics.

Exclusion Criteria

(i) Inability to swallow pills

(ii) Inability to communicate in English or native language in the absence of an interpreter

(iii) Current use of an anticholinergic

(iv) Hypersensitivity to either acetaminophen, HBB, or applesauce vehicle

(v) Treating physician’s suspicion (by clinical evaluation or diagnostic results) of appendicitis, constipation, hemodynamic compromise, peritoneal inflammation, foreign body or toxin ingestion, biliary pathology, vaso-occlusive crisis, genitourinary disease, gastrointestinal reflux, bowel obstruction, pancreatitis, gross GI bleeding, abdominal neoplasm, Henoch-Schonlein purpura, or pregnancy;

(vi) Self-reported administration of acetaminophen or HBB within 6 hours of screening

(vii) Abdominal trauma within 48 hours of screening

(viii) Medical record evidence of congenital renal or genitourinary anomaly, bowel obstruction, abdominal surgery, myasthenia gravis, hepatobiliary disease, acute angle closure glaucoma, chromosomal abnormality affecting the abdominal viscera, inflammatory bowel disease, celiac disease, pelvic inflammatory disease, abdominal neoplasm, or neutropenia;

(ix) Previous enrollment in the trial

Randomization

The randomization list was generated using a computer-based random number generator (http://www.randomization.com).

Allocation Concealment and Implementation of Randomization

Allocation concealment was performed using sequentially numbered, opaque, sealed envelopes. Preparation of interventions kits, randomization, and allocation concealment was pharmacy controlled. Interventions were administered by the bedside nurse.

Interventions

Due to perceptible differences in volume, consistency, and taste, we employed a *double-dummy* approach as follows: Participants were randomized in a 1:1 allocation ratio with block sizes of 4 or 6 to either single-dose:

(i) oral HBB 10 mg tablet (Boehringer Ingelheim, Burlington, Ontario) plus placebo acetaminophen liquid (Perrigo, Allegan, Michigan) or

(ii) oral acetaminophen 15 mg/kg liquid, maximum 975 mg (McNeil, Markham, Ontario) plus placebo HBB tablet (Perrigo, Allegan, Michigan).

The dose of HBB was based on previous methodology (4) and given with a teaspoon of applesauce. If the patient vomited within 30 minutes of receiving the intervention, another dose was given.

Permissible Co-Interventions

Rescue analgesia (not acetaminophen or HBB) was permitted at any time.

Discontinuation

Circumstances that may warrant termination or suspension of the intervention included, but were not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Participants were free to withdraw from participation in the study at any time upon request. However, data accrued from the participant to the time of withdrawal were retained by the investigators for analysis. An investigator or treating physician may have discontinued or withdrew a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurred such that continued participation in the study would have been detrimental to the health of the participant
- If the participant was found to meet an exclusion criterion (either newly developed or not previously recognized) that precluded further study participation

Adherence

To ensure adherence to the protocol, viability of the drug delivered and participant safety, at any given time the kits with the drug intervention were restricted to research personnel only in the ED. The interventions were labelled as Drug A or B. Each intervention kit contained a real drug and placebo (HBB 10 mg tablet and placebo acetaminophen suspension OR placebo HBB tablet and acetaminophen 15 mg/kg suspension (maximum 975 mg)). The RA identified the next group assignment in the allocation sequence, calculated the amount of drug that needed to be administered based on the participant's weight, and confirmed with the bedside nurse that the

calculations were correct. This system of double verification ensured that the participant received the correct dose and also ensured participant safety and protocol adherence. Once the calculation was verified, the bedside nurse drew up and administered the interventions.

Blinding

Blinded parties included the participant, caregiver, ED personnel, and all members of the study team excluding the pharmacist. Unblinding was to be performed by pharmacy in the event of a serious adverse event where the treating physician believed that awareness of group assignment would have changed management. In the unlikely event the patient developed a serious adverse event (SAE), an adverse event form and note-to-file were to be completed by the PI or their designate.

Data Collection

Outcome data were obtained by the RA using an iPad hosting the Research Electronic Data Capture (REDCap) platform (5). Pain scores, caregiver satisfaction, length of stay, disposition, rescue analgesia, and adverse effects in the ED were recorded at ED discharge. Recidivism and adverse effects post-discharge were recorded using a standardized telephone survey conducted by the RA 72-hours after ED discharge (Appendix II). The following demographic data were collected from the participant or the EMR in the ED or upon discharge if they were admitted to hospital: 1) characteristics of the pain 2) age 3) sex 4) analgesia prior to arrival 5) discharge diagnosis 6) length of stay. Self-reported pain was measured using a 100 mm VAS embedded into the REDCap project. Pain scores were obtained immediately prior to the intervention and at 15, 30, 45, 60, and 80 minutes post-intervention. Adverse effects were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) (6) and recorded based on (i) participant report from a drop-down list with an open-ended component, (ii) caregiver report

from a drop-down list with an open-ended component, and (iii) nursing records. Caregivers were asked to rate their level of satisfaction with the child's pain management using a 5-item Likert scale.

Data Management

Data management services were provided by Lawson Health Research Institute. All data were entered into a single study-specific REDCap project and was managed according to Lawson's specifications. Selected data elements were validated electronically on an ongoing basis throughout the study and any discrepancies were assigned to members of the study team for resolution. REDCap includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

Primary Outcome

Self-reported pain at 80 minutes post-intervention using a 100 mm VAS (7), reflecting the time to peak plasma concentration of HBB (8) and acetaminophen's onset of action (60-90 minutes) (9, 10).

Secondary Outcomes

(i) Need for rescue analgesia

(ii) Adverse effects

(iii) Proportion of children with a VAS score < 30 mm post-intervention, the target for effective analgesia specified by the WHO (11).

Other Endpoints

(i) Caregiver satisfaction with pain management using a five-item Likert scale (1-very unsatisfied; 2-somewhat unsatisfied; 3-neutral; 4-somewhat satisfied; 5-very satisfied)

(ii) Pain scores at 15, 30, 45, and 60 minutes post-intervention

(iii) Recidivism to a health care provider

(iv) Missed surgical diagnoses within 72-hours of ED discharge

(v) Length of stay

(vi) Disposition

(vii) Time to achieve a 20% reduction in pre-intervention pain score. (Appendix).

Schedule of Activities

	Study Period										
	Index Emergency Department Visit										
Time Point	**Confirm Eligibility**	**Pre-intervention**	**Time zero**	**15 min**	**30 min**	**45 min**	**60 min**	**80 min**	**Discharge**	**Follow up at 72 hours**	**End of the study**
Patient screening	X										
Obtaining consent +/- assent		X									
Enrollment	X	X									
Randomization		X									
Interventions			X								
Data Collection		X							X	X	
Study completion	X										X

Sample Size

We used a minimal clinically important difference (MCID) of 13 mm on the VAS based on a derivation (12) and validation cohort (13) and an adult ED study of HBB and acetaminophen for abdominal pain (14). With a standard deviation (SD) of 10 mm, 112 children per group were required to detect a difference at the 5% two-sided level of significance with 80% power. The sample size was increased to account for dropouts giving a rounded sample size of 115 participants per group (15). Data were analyzed using the SPSS statistical software package (version 24, IBM SPSS™, New York, NY). P values less than 0.05 were considered statistically significant.

Analysis

Analyses of efficacy outcomes were based on intention to treat. We assumed no change in pre-intervention pain score for participants who did not report the 80-minute VAS score. Analysis of adverse effects and caregiver satisfaction were based on participants who received the intervention. Inferential statistics were performed on primary and secondary efficacy outcomes. Means and standard deviations (SD), frequencies and percentages, and medians and interquartile ranges were used to summarize ratio, categorical, and ordinal data as appropriate, respectively. Pain scores at 80 minutes were compared using linear regression adjusting for pain score immediately prior to the interventions. Time to achieve a 20% reduction in pre-intervention pain score was reported using a Kaplan-Meier survival analysis. Categorical variables were compared using the Pearson's chi-square test. Data were analyzed using SPSS (version 24, IBM SPSS™, Armonk, NY). P values less than 0.05 were considered statistically significant.

Patient Engagement

We used a five-member focus group of caregivers of children with abdominal pain to inform the terminology for describing colicky abdominal pain, lower age limit for swallowing pills, and the wording of consent and assent forms. Activities were conducted in person and over email.

Data monitoring

A two-member data safety monitoring board (DSMB) was created prior to enrollment of the first patient and was independent of the study sponsor. The DSMB met when 25%, 50% and 75% of the participants were been recruited and as needed to assess safety.

Data Safety Monitoring Board

Team Member	**Rules and Responsibilities**
Dr. Michael Grattan Paediatric Cardiologist, Department of Paediatrics, Western University	DSMB Chair
Dr. Shruti Mehrotra, Paediatric Emergency Physician, Department of Paediatrics, Western University	DSMB member

The DMSB operated under the rules of an approved charter of reference that was reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needed to assess was defined. The DSMB provided its recommendations to the PI and the REB, and to Health Canada if requested. The DSMB, in collaboration with the research team, established safety stopping rules prior to trial initiation. The decision to stop the trial for safety reasons was left to the discretion of the DSMB. The DSMB had decided to stop the trial if there were concerns regarding safety due to study participation and not solely limited to the intervention. There were no interim analyses performed.

Reporting Adverse Events

The frequency of adverse effects was recorded by the RA based on (i) participant report from a drop-down list with an open-ended component, (ii) caregiver report from a drop-down list with an open-ended component, and (iii) nursing records. Enrolled participants were telephoned by an RA at 72 hours of discharge to assess for late adverse effects and return visits for surgical diagnoses. During the study, participants received standard monitoring by the bedside nurse of oxygen saturation, blood pressure, respiratory rate, and heart rate by the attending nurse and physician every 30 minutes as per the usual standard of care. The usual standard of care also included monitoring by the health care team for the presence of an adverse drug reaction for the duration of the visit. As there are no consistently documented adverse effects from a single dose of either HBB or acetaminophen, there were no anticipated risks to participants involved in the study. However, there were theoretical risks to HBB, being an anticholinergic medication and included dry mouth, light sensitivity, tachycardia, urinary retention, constipation, nausea, vomiting, dry skin. These have been described, albeit infrequently, and only in patients taking concomitant anticholinergic medications and these patients were excluded from participation. Acetaminophen at supratherapeutic doses had a theoretical risk of acute hepatic injury so we excluded patients with known liver disease from participation. The PI planned to report all unexpected SAEs to Health Canada within 15 calendar days after becoming aware of the event. For death or life-threatening events, the PI planned to file this report within 7 calendar days after the becoming aware of the event. In the latter case, the PI planned to file a follow-up report within 8 calendar days. We planned to submit all AEs, in accordance with the DSMB safety monitoring plan, to the DSMB. We planned to follow all patients with SAEs until satisfactory resolution or until the PI deemed the event to be chronic or the participant was stable. The PI was

responsible for notifying Health Canada of any fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the PI's initial receipt of the information. The PI was also responsible, within 8 days after having informed Health Canada of the adverse drug reaction, for submitting as complete as possible, a report which included an assessment of the importance and implication of any findings. In addition, where the adverse drug reaction was neither fatal nor life-threatening, the PI was responsible of notifying Health Canada and the REB of the event and any potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the PI determined that the information qualified for reporting. A completed Adverse Drug Reaction (ADR) Expedited Reporting Summary Form was to be attached to the front of the completed ADR report (suggested ADR report format: Suspect Adverse Reaction Report - CIOMS form of the Council for International Organizations of Medical Sciences (CIOMS).

Possible but rare adverse events related to the intervention are:

(i) Any reaction consistent with an acute hypersensitivity reaction that encompassed criteria for anaphylaxis (rash plus any one of the following: syncope or vomiting or difficulty breathing)

And adverse events related to the underlying pathology behind the participant’s presenting complaint of abdominal pain:

(ii) Severe abdominal pain and distension

The occurrence of these events was to be managed as per the usual standard of care in the ED setting. Post discharge, all participants were asked to return to their nearest ED or phone the PI at the number listed in the Letter of Information (LOI) should they suspect an ADR. A list of

possible ADRs was provided in the LOI. At discharge, participants were reminded of these risks and what to do if an adverse event was suspected.

Research Ethics Approval

The protocol, informed consent form(s), recruitment materials, and all participant materials were submitted to the REB for review and approval. Approval of both the protocol and the consent form was obtained before any participant was enrolled. As stated by the Western Research Ethics Board (REB), the Office of Human Research Ethics (OHRE) manages the approval and monitoring process for the use of humans in research at Western University, Lawson Health Research Institute and its affiliated hospitals and research institutes. All research involving humans conducted by faculty, staff or students at Western or its affiliated hospitals or research institutes must be approved by a Western-sanctioned review board. Once ethics approval is obtained a final approval from Lawson quality assurance team is issued and the clinical trial is allowed to start.

Protocol amendments

Amendments to the protocol were made regarding use of the VAS as the sole measure of pain, use of the EMR to follow participants unable to be reached by telephone, and addition of exclusion criteria for participants who were suspected to have abdominal pain due to a specific etiology. The first two amendments were made after the first patient was enrolled and the third amendment was made after three patients were enrolled. All amendments were reviewed and approved by the REB and Health Canada before the changes were implemented. All changes to the consent form were approved by the REB.

Consent / Assent forms

As per our REB requirements and Health Canada guidance, children at least 7 years of age were able to provide consent depending on the capacity to understand the implications of participation and the nature of the study itself. Considering these two relevant points we obtained assent from all children at least 7 years of age and informed consent, in the absence of a caregiver, from those considered by the treating physician a mature minor.

Confidentiality

Participant confidentiality and privacy were strictly held in trust by the PI and research staff. Therefore, the study protocol, documentation, data, and all other information generated were held in strict confidence. No information concerning the study or the data were released to any unauthorized third party without the prior written approval of the sponsor. All research activities were conducted in as private a setting as possible. The study monitor, other authorized representatives of the sponsor, representatives of the REB, or regulatory agencies were able to inspect all documents and records required to be maintained by the PI, including but not limited to, medical records and pharmacy records for the participants in this study. The study participant's contact information was securely stored with the PI in the ED for internal use during the study. All records will be kept in a secure location for 25 years as per Health Canada requirements. De-identified study participant research data, which for purposes of statistical analysis and scientific reporting, were stored in REDCap at Lawson Health Research Institute. This data did not include the participant's contact or identifying information. Rather, individual participants and their research data were identified by a unique study identification number. An iPad was used to enter data into the REDCap data collection system. No information was stored

on the iPad. A custom REDCap database was built for this project to collect the necessary information. Data is stored on a centralized server located at Lawson Health Research Institute.

Declaration of interest

All members of the research team including the PI did not have any conflicts of interest or financial interests to declare.

Access to data

The PI was be responsible for retaining (archiving) all essential study documents that individually or collectively permitted the evaluation and conduct of the study and the quality of data, in accordance with International Conference on Harmonization Good Clinical Practice (ICH-GCP) and applicable regulatory requirements. All study documents, including source, were stored in a confidential location with secured and limited access. All electronic records and data sets were encrypted and password protected with access only permitted only by the PIs. Results were not be reported in a way that identified any individuals. All study related documentation are retained in accordance with Health Canada's Food and Drug Regulations for 25 years and per the investigational site's institutional record management and retention policies. No records will be destroyed without the written consent of the Qualified Investigator and/or Sponsor. Paper data (e.g. copies of consent and assent forms) are stored exclusively in the PI's research office in a locked cabinet.

Ancillary and post-trial care

Post discharge, all participants were asked to return to their nearest ED or phone the PI at the number listed in the LOI should they suspect an ADR. A list of possible adverse reactions was provided in the LOI. At discharge, participants were reminded of these risks and what to do if an

adverse event was suspected. Participants were telephoned by a research assistant 72 hours after discharge to assess whether or not any adverse drug reaction has occurred.

Dissemination policy

Our findings were submitted for publication to a high impact peer-reviewed journal and the study protocol was registered on clinicaltrials.gov. We presented our findings at local research days and academic meetings within 18 months of study completion.

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