Sterile water injections for relief of labour pain (the SATURN trial)

Study protocol for a randomised controlled trial

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Sterile water injections for relief of labour pain (the SATURN trial): study protocol for a randomised controlled trial

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Abstract

Background: Up to 80% of women use some form of pharmacological analgesia during labour and birth. The side effects of pharmacological agents are often incompatible with the concurrent use of non-pharmacological pain-relieving strategies, such as water immersion, ambulation and upright positioning, or may have negative effects on both the mother and foetus. Sterile water injections given into the skin of the lumbar region have been demonstrated to reduce back pain during labour. However, the injections given for back pain have no effect on abdominal contraction pain. The analgesic efficacy of sterile water injections for abdominal pain during childbirth is unknown. The injections cause an immediate, brief but significant pain that deters some women from using the procedure. This study aims to investigate the use of water injections given intradermally into the abdomen to relieve labour contraction pain. A vapocoolant spray will be applied to the skin immediately prior to the injections to reduce the injection pain.

Methods: In this pragmatic, placebo-controlled trial, 154 low-risk women in labour at term with a labour pain score ≥ 60 on a 100-ml visual analogue scale (VAS) will be randomly allocated to receive either six injections of sterile water or a sodium chloride 0.9% solution as a placebo (0.1–0.3 ml per injection). Three injections are given along the midline from the fundus to the supra-pubis and three laterally across the supra-pubis. The primary outcome will be the difference in VAS score 30 min post-injection between the groups. Secondary outcomes include VAS score of the injection pain on administration, VAS score of labour pain at 60 and 90 min and maternal and neonatal birth outcomes.

Discussion: Access to effective pain relief during labour is fundamental to respectful and safe maternity care. Pharmacological analgesics should support rather than limit other non-pharmacological strategies. Sterile water injections have the potential to provide an alternative form of labour pain relief that is easy to administer in any labour and birth setting and is compatible with other non-pharmacological choices.

Trial registration: ANZCTR ACTRN12621001036808. Registered on 05 August 2021

Keywords: Sterile water injections, Labour pain, Analgesia, Randomised controlled trial

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Administrative information

Title {1}	Sterile water injections for relief of labour pain (the SATURN trial): study protocol for a randomised controlled trial
Trial registration {2a and 2b}	anzctr.org.au (ACTRN12621001036808) Date submitted: 22/06/2021. Date registered: 05/08/2021.
Protocol version {3}	Version 2 15 July 2021
Funding {4}	The trial was funded by the Australian Government Department of Health Medical Research Future Fund (APP2006488)
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Name and contact information for the trial sponsor {5b}	Dr. Nigel Lee School of Nursing Midwifery and Social Work University of Queensland St Lucia, Queensland, Australia 4072 nigel.lee@uq.edu.au
Role of sponsor {5c}	The University of Queensland is the trial sponsor. Final decisions related to the study design, data collection, analysis, interpretation, and manuscript preparation were made by the investigator team.

Background {6a}

In countries such as Australia and the UK, up to 80% of labouring women use some form of pharmacological analgesia [1, 2]. Current options for pharmacological analgesia in labour have changed little in past decades with the most common choices being opioids, nitrous oxide inhalation and neuraxial (epidural) analgesia. The analgesic effectiveness of opioids such as morphine and pethidine is minimal with most women continuing to report moderate to severe pain [3]. Opioids are more likely to provide drowsiness than analgesia which has highlighted the ethical problem of primarily providing sedation in response to a woman's request for pain relief [4]. Opioids readily cross the placenta and are found in breast milk. The metabolism of pethidine results in the formation of norpethidine, which is associated with neuronal depression in the neonate up to 60 h post-birth and feeding difficulties for up to 6 weeks postpartum [5, 6].

The analgesic effectiveness of nitrous oxide varies from no difference to the placebo to similar to that of opioids [7]. Whilst generally considered safe, recent studies have highlighted metabolic, oxidative, genotoxic and transgenerational epigenetic effects from prolonged exposure. A 1 to 3 h exposure to 50% nitrous oxide (a common dose during labour) inactivates methionine synthase in the mother and foetus which can take 3 to 5 days to recover. This increases the potential for haematological disorders such hypercoagulation, particularly in vitamin B_{12}-deficient women [8].

In high-income countries, epidurals are used by up to 70% of labouring women [1, 9]. Epidurals have been shown to provide more effective analgesia than opioids [10]. Whilst generally considered safe, epidurals can have immediate, medium and possibly long-term side effects. Epidurals are strongly associated with maternal fever during labour resulting in increased use of antibiotics [11], prolonged labour and assisted birth (vacuum extraction or forceps) [12].

Many women will use a combination of pharmacological and non-pharmacological strategies to achieve personal and psychological control over the pain they are experiencing, rather than seeking a total elimination of pain [13]. All of the current pharmacological agents are largely incompatible with non-pharmacological options, particularly those involving ambulation, upright positions or water immersion [14]. Both nitrous oxide and opioids can result in sedation and impaired balance that may increase the risk of falls injuries. Epidurals require intravenous cannulation, fluid administration, urinary catheterisation and continuous foetal monitoring. These restrict mobility and reduce a woman's ability to adopt favourable positions for labour and birth.

A recent placebo-controlled trial demonstrated the efficacy of sterile water injections into the lumbar region to relieve back pain in labour with no detrimental side effects [15]. Back pain in labour is different and may occur independently from abdominal labour pain [16]. Furthermore, the injections given into the lumbar region for back pain have no effect on abdominal contraction pain [15, 17]. Injections of sterile water are acutely painful for a brief period, and this is known to act as a deterrent to both women and clinicians [18, 19]. Theoretically, the acute pain associated with the injection (noxious stimulus), tissue distension and increased osmotic pressure stimulate gate control of pain and endorphin release to reduce pain [20, 21]. A moderate reduction in injection pain, through the administration of one rather than four injections, still results in significant analgesia though for a shorter duration [17]. Though no

reliable method to achieve a consistent reduction in overall injection pain is currently in use [17]. A non-placebo exploratory trial and case study suggests the potential for using water injections to relieve abdominal labour pain [22, 23].

Vapocoolant sprays consist of rapidly evaporating solvents that quickly reduce skin temperature to produce a numbing effect and result in a moderate reduction in pain scores [24]. The only reported side effects are the cold sensation and occasionally mild transient erythema at the treated sites [24].

We aim to test the effectiveness of sterile water injections given into the abdomen to relieve labour contraction pain. We will also apply a vapocoolant spray immediately prior to the injections to reduce the injection discomfort.

Methods

Study design {8}

This will be a pragmatic randomised placebo-controlled superiority trial specifically designed to provide evidence of the efficacy of water injections to relieve abdominal labour pain. The following provision of informed consent participants will be randomised to receive either water injections (intervention) or normal saline injections (control). For both groups, pre-injection preparation with a vapocoolant spray will occur. Participants will have access to any form of standard care including combinations of currently available pharmacological and non-pharmacological options. The participant flow is demonstrated in Fig. 1.

Study setting {9}

The trial will be conducted at a tertiary maternity unit in Brisbane Australia providing labour and birth care for approximately 5000 women annually. The research site provides both birth centre and standard labour and birth care.

Study population and recruitment {10}

We plan to recruit and consent provisionally eligible women in the late antenatal period (36–37 weeks). Whilst this may include women who are either ineligible at the onset of labour, or remain eligible but decline participation, this strategy will reduce the need to rely on clinical staff, in the birth suite and birth centre, to identify, screen, provide participant information and complete consent documentation whilst also providing care. This also minimises the ethical issue of recruiting and consenting in labour when pain and/or effect of medications may impact the woman's capacity to consent to participation in research. The study site offers a number of models providing care to women likely to meet the inclusion criteria. These are broadly defined as midwifery and general practitioner (GP) shared care. Midwifery care models are provided by the Birth Centre and Midwifery Group Practices (MGP). Women attending GP shared care all return at 36 weeks gestation, providing an opportunity to discuss the trial and participation. Women attending Birth Centre and MGP antenatal clinics will be approached during their 36–37 week visits.

The eligibility criteria consist of ≥ 16 years of age, singleton cephalic (head down) pregnancy, ≥ 37 weeks

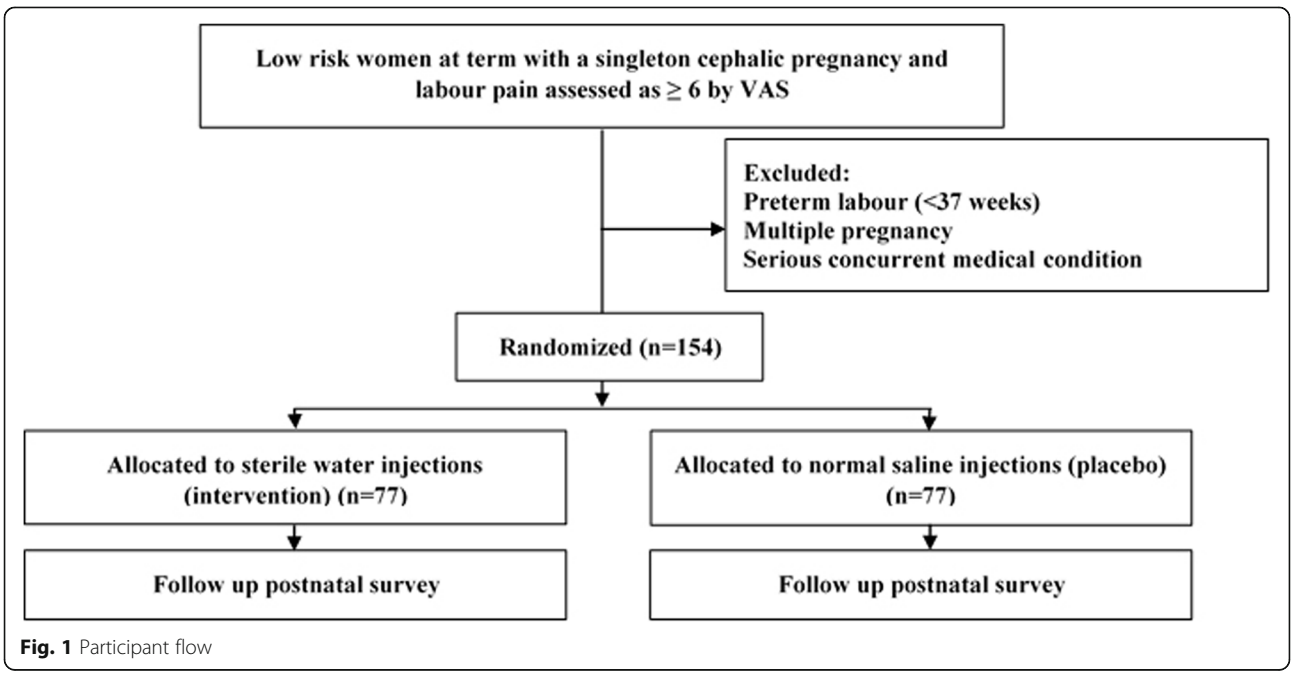

Fig. 1 Participant flow

gestation, spontaneous or induced labour, no serious concurrent medical conditions (pre-eclampsia, coagulopathy, diabetes other than diet controlled), cognitively capable of providing consent and able to read and understand instructions written in English. Upon admission to the birth suite, randomisation will occur when the participant's self-assessment of labour pain ≥ 60mm (visual analogue scale [VAS] 0–100mm: 0 = no pain, 100 = worst conceivable pain) and requesting pain relief.

Randomisation and blinding {16, 17}

Randomisation schedules will be prepared by a statistician independent of the study using computer-generated pseudo-random numbers, using varying block sizes. Identical ampoules of either normal saline or sterile water will be pre-prepared by the study site pharmacy and packed in opaque plastic packets and arranged based on the allocation schedule. Following confirmation of consent, two midwives will remove the next ampoule in sequence and administer the injections. Normal saline for injection 0.9% will be used as the placebo solution. Normal saline is an active placebo resulting in some minor injection discomfort and some degree of analgesia, it has been used successfully in previous placebo-controlled trials [15, 25]. The control arm (normal saline with vapocoolant) will reduce the chance of participant unbinding as all women will experience cooling effect of the vapocoolant and still have an equal chance of water or normal saline injections.

Procedures {11a, b}

Participants in the intervention groups will receive intradermal injections of 0.1–0.3 ml of sterile water into six anatomical points on the abdomen (Fig. 2). The volume required to be injected is based on the visual estimation of the resulting blister or 'bleb'. If the needle is inserted beyond the intradermal layer, the bleb does not occur and the needle may require repositioning to achieve the correct anatomical depth. The location of the injections is based on a previous RCT of water injections versus acupuncture and early studies that used intradermal injections of local anaesthetic into the abdomen to relieve pain in labour [22, 26, 27]. These studies suggested that injections given in a line extending medially from the fundus to the suprapubic area and extending laterally from the suprapubic region will produce an effective analgesic response. As the experience and location of contraction pain vary considerably, the precise location and number of injections may vary based on the areas of greatest discomfort indicated by the woman. Up to three repeat courses of injections will be provided for women who request them. Data items such as the location of injections, VAS and duration of effect will be collected for the initial and repeat injections. All midwives administering water injections will be credentialed in this technique using a competency-based assessment that was used successfully in our previous trials [22, 28].

Participants in the control group will receive intradermal injections of 0.1–0.3 ml of normal saline 0.9% for injection into the abdomen as previously

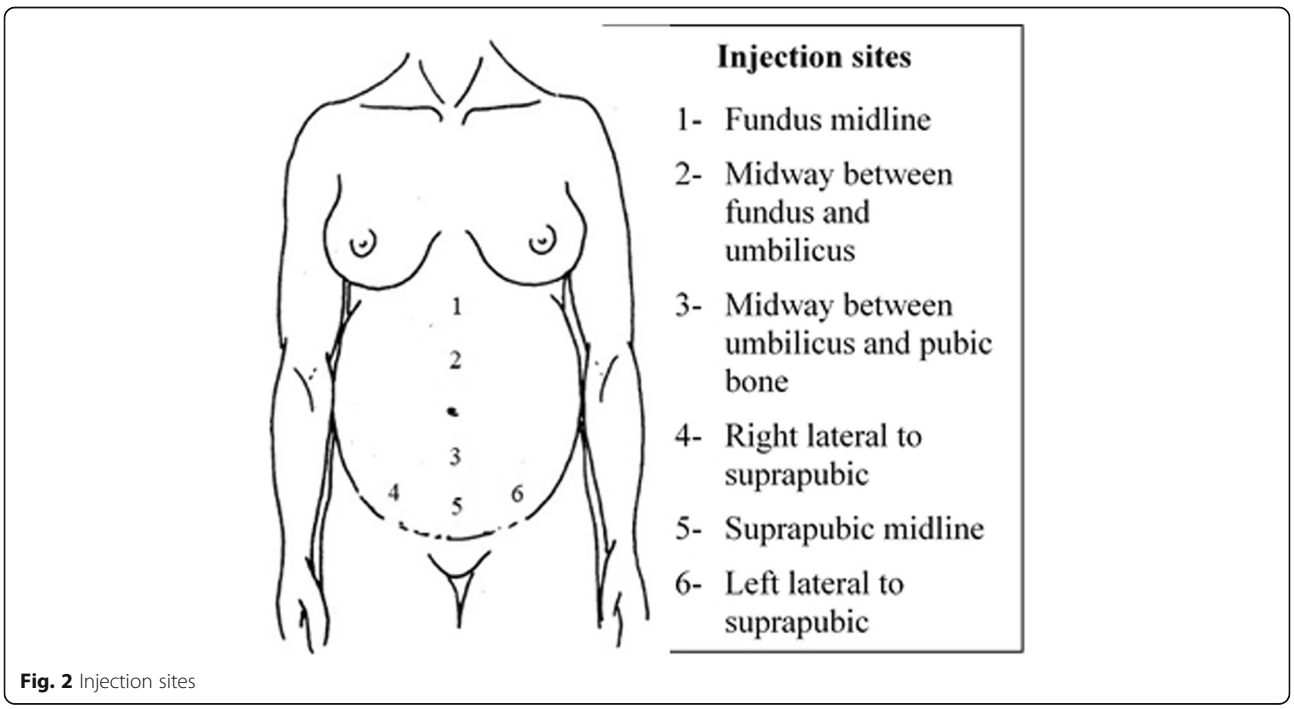

Fig. 2 Injection sites

described. All other components of the administration will be the same as the intervention group.

Both groups will also receive skin preparation immediately prior to the injections using the vapocoolant spray PainEase® manufactured by Gebauer. PainEase® spray contains 1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane which are non-flammable and unlike ethyl chloride are not absorbed through the skin and therefore safe to use in pregnancy. The cooling effect occurs through rapid evaporation. PainEase is registered with the Australian Therapeutic Goods Administration as a vapocoolant topical anaesthetic available to the general public. The injection points will be sprayed with PainEase® spray at a distance of 12 cm from the skin for a period of 5 to 8 s immediately prior to administering the injections.

Outcomes {12}

The primary outcome for the trial is the mean difference in VAS scores of labour pain between the intervention and control groups at 30 min following the administration of the injections. Secondary outcomes include the number of women experiencing an at least 30% or 50% reduction in pain following the injections. This is the measure of analgesic effectiveness recommended in the Cochrane Review of water injections for back pain in labour [29]. Other secondary outcomes are detailed in Table 1.

Postnatal survey

Following birth, all participating women will be asked to complete an electronic survey of their experiences of the injections and spray they received in the context of their labour and birth.

The survey is based on versions used in our previous studies and measures levels of satisfaction with pain relief, relaxation, likelihood to use in a subsequent labour and recommend to other women, most positive and negative aspects of the trial experience [15]. For women who remain in hospital following their birth, the survey will be completed on a tablet device. For those women opting for early discharge or discharged on weekends, a link to the survey will be emailed with follow-up contact from a research assistant. Survey data will be identifiable only through the allocated study participant code to enable matching with the allocated group in the clinical trial.

Sample size {14}

We have calculated the sample size based on the recommended minimal clinically significant reduction in VAS scores: 10 mm difference on a 100-mm VAS score between intervention and placebo [30]. To demonstrate a 10-mm reduction (SD 20 mm) in VAS scores with 80% power and 0.05 significance (two-sided) would require 64 participants per group. Based on previous studies, we estimate an attrition of 20% due primarily to women giving birth or requesting epidural analgesia prior to the measurement of the primary outcome. The total sample size required would be 154 participants, 77 per trial group.

COVID-19 safe data collection {18, 19}

We have designed a method of data collection that is both COVID-19 safe and compatible with the realities of providing care during labour and birth. Data will be entered directly into a REDCap database using an iPad specifically configured for the trial. Participants will carry a card that contains a unique study number that once entered will link to an existing database entry. Following randomisation, the attending midwife will enter minimal required data (e.g. allocation code, results of most recent vaginal examination). The iPad will then be placed in a waterproof protective sleeve that will allow the woman to use touch screen 'sliders' to indicate their level of pre-treatment, injection and post-treatment on a 100-mm VAS scale. The use of digital VAS has been validated against paper versions [31]. The protective sleeve will prevent device contamination from body fluids, shower and bath water and can be disposed of following data entry. Direct data entry will reduce data transcription errors contributing to trial fidelity. Each midwife will have a unique code to identify them as responsible for data entry in keeping with Good Clinical Practice (GCP) principles. A horizontal VAS is used to measure the primary outcome, the experience of self-reported pain scores. The VAS is sensitive to pain intensity, validated for use in research and most individuals have no difficulties using it [32]. Demographic and clinical data will be extracted from the research site's perinatal database. The final dataset will only be accessible to investigators participating in the data analysis as specified within the trial agreements

Data analysis {20}

All women who underwent randomisation and for whom primary outcome data is available will be analysed in their allocated treatment groups (i.e. intention to treat). Randomisation should ensure that any baseline differences between the groups occur by chance. To control for cluster effect of repeated measurement, a linear mixed-model analysis will be conducted to investigate the difference in mean VAS score pre- and post-intervention. Categorical data will be analysed with chi-squared tests, and non-repeated continuous variables will be analysed with *t*-tests if normally distributed or Mann-Whitney *U* test if non-normally distributed. Additional multivariable analysis will be employed if baseline

Table 1 Schedule of enrolment, interventions and assessments

Time point**	Study period						
	Enrolment	Allocation	Post-allocation				Close-out
			Time periods after injection			1-14 days post-birth	From perinatal database
			30 min	60 min	90 min		
Enrolment							
Eligibility screening	X	X					
Signed consent form	X						
Randomisation		X					
Interventions							
Sterile water injection		X					
Normal saline placebo injection		X					
Vapocoolant spray		X					
Assessments							
Cervical dilation		X					
VAS of labour pain prior to injections		X					
VAS of injection pain		X					
VAS of labour pain post injection			X	X	X		
At least 30% reduction in VAS of pain			X				
At least 50% reduction in VAS of pain			X				
Pharmacological analgesia use		X					X
Non-pharmacological analgesia use		X					X
Duration of labour							X
Augmentation of labour							X
Mode of birth							X
Estimated blood loss at birth							X
Apgar scores							X
Type of neonatal resuscitation							X
Admission to nursery							X
Duration of hospital stay							X
Breastfeeding at discharge							X
Postnatal survey						X	
Economic analysis							X

differences are noted between the two groups. Treatment effects will be presented as the mean difference or relative risks with 95% confidence intervals. All study outcomes will be analysed using a two-sided P value of < 0.05 to indicate statistical significance.

For the postnatal survey data, descriptive statistics will be calculated for all variables, including the mean, median, standard deviation, range, and percentages as appropriate. Free text responses will be analysed thematically.

Economic analysis {20}

A cost-effectiveness analysis will be undertaken to compare costs and outcomes between the intervention and placebo groups from the perspective of the health system. The approach to the identification, measurement and valuing resource use will follow a similar approach to that which we have used in previous studies [15]. Information about resource use and costs will be collected at the research site. In the case of the intervention, resources to be identified and measured will include those associated with the establishment of the intervention (staff training, development of educational resources and credentialing) and staff time required for administration. Costs will be allocated to the relevant resource items using appropriate values. For example, staff time will be costed using hourly award rates plus on-costs, and the costs of the length of stay and complications from admission to discharge of hospital will be estimated using appropriate diagnostic-related groups. The outcome for the economic evaluation is VAS pain score difference between the two groups. The incremental cost-

effectiveness ratio will be calculated, and the cost-effectiveness acceptability curve will be graphed to summarise the uncertainty of cost-effectiveness according to different willingness to pay.

Monitoring and reporting of risks {21}

Standard operational procedures (SOPs) will be developed for the risk management and reporting based on those used in previous clinical trials [15]. The SOPs will detail the role responsibilities and processes for risk reporting and be reviewed and approved by a Data Safety Monitoring Board (DSMB) and Trial Executive Committee (TEA). The DSMB members will be independent of the study and consist of an obstetrician, midwife, statistician and a consumer representative. The TEA will consist of the chief investigators and trial manager. Each SOP will define and stratify any potential risk according to the University of Queensland Risk Level Calculator, which assesses the 'likelihood' versus the 'consequences' of risk and thereby assigns ratings from 1 = low to 5 = very high. The SOPs will also outline the standardised response and reporting procedure per risk level. Emergency code breaks for trial allocation will be available 24/7 if required. All adverse events will be reported and actioned immediately. The DSMB will manage the risk register and recommend necessary modifications or termination of the trial. Code breaking (unblinding) is possible in the event of a serious unexpected adverse event that requires identification of the allocated intervention to progress treatment. A sealed envelope containing the allocation will be held onsite in a secure location and accessible 24 h a day.

Dissemination of findings {31}

The results will be reported in conferences or peer-reviewed journals. The results will also be shared with participants, healthcare professionals and the public through lectures or science handbooks.

Discussion

The provision of effective pain relief is a fundamental aspect of respectful, safe care during labour and birth [33]. Ideally, pharmacological analgesic options should support, rather than limit, women's choices and plans to manage the pain of labour and be free of side effects that may negatively contribute to the experience and outcomes of labour. Currently, none of the commonly available pharmacological options achieves this. What is needed is an analgesic option that is simple to administer, effective in reducing contraction pain, largely free of side effects and compatible with non-pharmacological techniques. The use of sterile water injections has the potential to fulfil this need. The technical simplicity of sterile water injections makes it suitable for use in all maternity care settings and by many levels of health care providers.

Our study will be the first placebo-controlled randomised trial to assess the use of sterile water injections to relieve the abdominal contraction pain of labour. The study design has the methodological strength to provide high-level evidence efficacy and safety. The trial will also initiate the use of a vapocoolant spray to mitigate the pain associated with the administration of water injections and assess the impact of this approach on the acceptability of the procedure. The postnatal survey will assess women's satisfaction with the allocated treatment and the likelihood to reuse the same method in subsequent pregnancies. This experience of using water injections for abdominal labour pain will be further explored in proposed qualitative studies. The economic analysis will assess the patterns and levels of resource utilisation associated with each participant across the two arms of the study. The combination of data and analysis will assist in contextualising the findings from the RCT and enhance the understanding of the potential role of water injections as a labour pain analgesic.

The successful completion of our trial will see a new use for one of the most widely available medical preparations as an analgesic, improved choice for women and more efficient use of health resources.

Trial status

Trial protocol version and date: version 2, 15 July 2021
Recruitment will commence on 4th April 2022
Recruitment to be completed by 30th April 2023

Abbreviations

GP: General practitioner; MGP: Midwifery Group Practice; VAS: Visual analogue scale; SOP: Standard operational procedure; DSMB: Data Safety Monitoring Board; GCP: Good Clinical Practice

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Authors' contributions

NL conceived the study and drafted the study protocol and manuscript. SK, LM, YG, LC and BB revised the study protocol, design and manuscript. YG calculated the sample size and devised the data analysis plan. All authors reviewed and approved the final manuscript.

Funding

The trial was funded by the Australian Government Department of Health Medical Research Future Fund (APP2006488). The funding body had no role in the design of the protocol and will not have any role in the conduct of the study including the interpretation of the data and preparation of the manuscripts for publication.

Availability of data and materials

The data from this study will be confidential until the database is closed at the end of the study. Following final publications, the database will be open to other researchers upon request in line with the National Health and Medical Research Council policy.

Declarations

Ethics approval and consent to participate

The study was peer-reviewed as part of the funding process. Ethical approval was provided by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/2021/QRBW/76389) and the University of Queensland Human Research Ethics Committee (2021/HE001769). The trial is registered at anzctr.org.au (ACTRN12621001036808), date submitted: 22/06/2021 and date registered: 05/08/2021. Important protocol modifications will be reviewed by the relevant ethics committees and updated on the trial register. All participants enrolled in the trial will provide informed written consent.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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