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Research Paper

Caesarean delivery rates and analgesia effectiveness following injections of sterile water for back pain in labour: A multicentre, randomised placebo controlled trial

Nigel Lee[a,c,*], Yu Gao[b,c], Sally L. Collins[d,f], Lena B. Mårtensson[e], Wendy Randall[f], Toni-Marie Rowe[g], Sue Kildea[b,c]

[a] School of Nursing, Midwifery and Social Work, University Of Queensland, St Lucia, Queensland, Australia
[b] Molly Wardaguga Research Centre, Charles Darwin University, Brisbane, Australia
[c] Mater Research Institute and School of Nursing, Midwifery and Social Work, University of Queensland, Australia
[d] Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom
[e] School of Health Sciences University of Skövde, Sweden
[f] Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom
[g] Women's and Children's Health Network, Adelaide, South Australia

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ABSTRACT

Background: About a third of women experience severe back pain during labour. Injecting small volumes of intracutaneous sterile water into the lumbar region can be used to relieve this pain, however the procedure is controversial and previous reviews call for high quality trials to establish efficacy. We evaluated the impact on birth outcomes and analgesic effects of sterile water injections.

Methods: A multicentre, double-blind trial undertaken between December 2012 and December 2017 in one British and 15 Australian maternity units. Women experiencing severe back-pain in labour were assigned (1:1) by an independently generated randomisation schedule stratified by site to injections of either sterile water or saline placebo. Participants and caregivers were blinded to group allocation. The primary outcome was caesarean delivery rate. Main secondary outcomes included at least 30% or 50% reduction in self-reported pain scores at 30, 60 and 90 minutes after treatment. Intention to treat analysis were used and the level of significance for the multiple clinical outcomes was set at $p<0.001$ with the Bonferroni correction applied. The study is registered with the ACTRN Registry number, ACTRN1261100022195

Findings: Between December 9, 2012, and December 15, 2017, 1166 women were recruited and randomised: 587 women received sterile water injections (SWI) and 579 a saline placebo. Seven women in the SWI group and 12 in the placebo group were excluded as consent was not completed, leaving 580 and 567, respectively, included in the analysis. The proportions of caesarean delivery were 17·1% (82 of 580) in the SWI group and 14·8% (82 of 567) in the placebo (RR 1·16, 95% CI 0·88–1.51; $p = 0·293$). At 30 min post treatment 60·8% (330 of 543) of women in the SWI group reported a 30% reduction in self-reported pain compared to 31·4% (163 of 520) placebo (RR 1·94, 95% CI 1·68–2·24; $p=<0·001$) and 43·3% (235 of 534) SWI reported a 50% reduction versus 18·1% (94 of 520) placebo (RR 2·39, 95% CI 1·95–2·94; $p=<0·001$). The analgesic effect of SWI compared to placebo remained significant at 60 and 90 min post-treatment. There were no significant differences in other maternal or neonatal outcomes.

Interpretation: Compared to placebo, injections of sterile water did not reduce rates of caesarean delivery. For the main secondary outcome of pain relief the intervention did result in significantly more women reporting at least 30% and 50% reduction in pain for up to 90 min. Water injections have no effect on birth outcomes though can be an effective treatment for the relief of labour-related back pain.

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1. Introduction

This randomised trial sought to provide conclusive evidence for the effect of sterile water injections (SWI) on caesarean delivery rates

* Corresponding author.
E-mail address: nigel.lee@uq.edu.au (N. Lee).

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Research in context

Evidence before this study

Current evidence from two systematic reviews, including a Cochrane review, examining the use of SWI for back pain in labour suggests administration may reduce back pain and caesarean delivery rates however results were not conclusive. The Cochrane review also reported a high risk of bias due to inadequately described allocation and blinding, and questioned the clinical relevance of mean VAS scores reported in all studies recommending instead a dichotomous outcome of an at least 30% or 50% reduction in self-assessed pain. These reviews called for a large randomised controlled trial to assess both the analgesic effect and impact on caesarean section rates.

Added value of this study

This study is the largest placebo controlled evaluation of the use of SWI in labouring women and first to report pain related outcomes using the recommended criteria for making a clinically relevant assessment of the analgesic effect. Whilst the primary outcome of a difference in the rate of caesarean delivery was not significant, the trial does provide definitive evidence for the safety and effectiveness of water injections on back pain in labour. Twice as many women in the water injection group reported a 50% reduction in pain at 30 min post treatment and rated the pain relief as 'very effective' compared to the placebo.

Implications of all the available evidence

The use of water injections to relieve back pain in labour does not reduce the incidence of caesarean delivery, or impact upon any other maternal or neonatal outcomes, clarifying the discrepancy in findings between the 2009 meta-analysis and the Cochrane review. The demonstration of an analgesic effect from water injections and safety for mother and baby has significant implications for its use to manage back pain in labour. Other than the transient pain of the injections, the procedure is free of side effects, low-cost and is suitable for use in a wide range of health care and low-resource settings.

and the relief of back pain in labour. A severe and often constant lower back pain occurs in approximately 30% of labouring women [1]. This type of back pain is believed to be associated with the stretching of the lumbosacral nerve plexus and compression of the viscera. The painful stimuli is not actually occurring in the lower back but is instead 'referred' there due to intercommunication in the dorsal horns of the spinal segments between the afferent fibres from the lumbosacral plexus and viscera, and the Aδ afferent fibres of the dermatomes of the lower back [2]. The combination of the intermittent contraction pain superimposed on the constant back pain leads many women to describe it as 'excruciating' [1] and the referred nature of the pain makes it difficult to treat. Where epidural analgesia is not available, the pain can lead to an extremely distressing, potentially traumatic, birth experience.

Sterile water, administered into the skin bordering the Michaelis Rhomboid, is regularly used in countries such as Sweden and Australia to relieve this type of back pain in labour. Intracutaneous (also called intradermal) sterile water causes a brief but significant pain at the site of the injection and is thought to act via the gating theory of pain, with the somatic stimulation from the injection site overwhelming the pain referred there from the nerve plexus and viscera [3–5]. This has led to it being described as using 'referred stimulation' to relieve referred pain [6]. It is a simple, inexpensive treatment which can be administered by a birth attendant with minimal training, making it ideal in situations where epidurals are not readily available such as midwifery-led units, the home or low resource settings. Transient pain has been associated with administration but no adverse events have been reported. However, small numbers, methodological issues and differences in administration techniques in previous trials has resulted in a lack of robust evidence to support the procedure [6]. Some national guidelines, for example the National Institute for Health and Care Excellence in the United Kingdom, also appeared to express concerns regarding safety specifically advising against the use of sterile water injections [7]. Furthermore, many healthcare providers are sceptical of the efficacy of the procedure and as a result it is not permitted in many institutions [8,9].

Labour related lower back pain is believed to be linked to foetal occipito-posterior position and labour dystocia, both of which are associated with higher rates of caesarean delivery [10]. A meta-analysis of randomised controlled trials (RCTs) comparing SWI to either a placebo or other forms of care (n = 828) reported not only pain-relief but also significantly lower rates of caesarean delivery in the sterile water group (4·6% vs 9·9%, Relative Risk [RR] 0·51, 95% Confidence Interval [CI]: 0·30–0·87) [11]. The authors highlight that the underlying mechanism for the reduction in caesarean delivery rate is unknown, however they speculate that the increased parasympathetic tone and relaxation of the pelvic musculature that is associated with the relief of pain, may facilitate the descent of the foetus. A more recent Cochrane review of only placebo-controlled trials reported rates of caesarean delivery of 4.4% with sterile water compared to 9.9% in the normal saline placebo groups (RR 1·31, 95% CI: 0·33–1·02) [6]. This did not reach statistical significance and had a smaller sample in the pooled analyses (n = 766) [6]. The Cochrane review also highlighted methodological issues in previous trials and recommended the use of a more robust outcome for pain-relief (at least 30% and 50% reduction in pain). No placebo-controlled trials of SWI for back pain in labour have reported outcomes in this format leading the review authors to recommend that whilst promising, further high-quality research was required to clearly demonstrate the analgesic efficacy of intracutaneous sterile water. There have been many calls to identify ways to reduce caesarean delivery rates [12] and SWI administration showed promise. We conducted the ICARIS (Impact on Caesarean sections following Injections of Sterile Water) trial to determine if the use of intracutaneous sterile water to treat back pain in labour would result in a reduced rate of caesarean delivery, and to measure the safety and analgesic effectiveness of the procedure based upon the Cochrane review reporting criteria.

2. Methods

2.1. Study design and participants

We conducted a pragmatic, multicentre, double-blind placebo controlled randomized trial. The study took place at 15 maternity units in Australia and one in the United Kingdom. Recruitment commenced on December 9th 2012 in four hospitals with further Australian sites added in 2013 and 2014, the UK site was commenced in 2016. Recruitment ceased on December 15th 2017.

Study sites provided pregnancy and labour care to between 3000 and 6500 publically insured women annually. Three sites provided SWI as standard care and provided women information antenatally regarding the procedure, if women at these hospitals specifically requested SWI for pain relief they were not offered inclusion in the study due to the possibility of receiving a placebo. At other sites where SWI was not standard care SWI was only offered in the context of the trial. All participants included in the analysis provided written informed consent.

The study protocol was approved by Royal Brisbane and Women's Hospital Human Ethics Review Committee for the Australian sites

and the South Central – Oxford B Research Ethics Committee for the UK site. The study protocol has been published previously [13].

Eligible women were 18 years of age or older with a singleton cephalic foetus between 37 and 41 weeks and six days gestation in either spontaneous, induced or augmented labour. Women experiencing back pain in labour self-assessed as being equal to or greater than seven on a verbal (1–10) pain scale were offered information about the trial. Previous studies of pain assessment have identified a score of seven or more on a 1–10 scale as equating to severe pain [14]. At this level the back pain was likely to be distinguishable from pain experienced elsewhere including uterine contraction pain. Women were excluded if they had previously had a caesarean delivery for any reason, significant co-morbidity, any contraindications to receiving injections (e.g. infection at the injection site, bleeding disorders) or used their health insurance to access labour care from a private obstetrician of their choice. In Australia, privately insured obstetric care had been associated with higher rates of caesarean delivery when compared to public [15]. Only one participating site admitted large numbers of privately insured women. At this site SWI were available as standard care for publically insured women only due to the general lack of support for the procedure from private obstetricians. This trial required consent from women in labour as the occurrence of back pain in labour cannot be predicted antenatally. If clinicians considered that the woman could not make an informed decision regarding participation in research for reasons such as, but not limited to, labour being too far advanced, progressing quickly or not coping with pain, their participation was not sought.

2.2. Randomization and masking

Women were randomly assigned (1:1) in permuted blocks of four to receive either injections of sterile water or a 0·9% sodium chloride solution (normal saline) placebo. Normal saline has been used as an active placebo in previous water injections trials as whilst it is transiently uncomfortable when the skin is pierced and a visible blister or 'bleb' is raised, the isotonic nature results in rapid painless absorption of the saline without having the longer lasting irritant properties of sterile water that are thought to impact the duration of effect [16,17]. Identical plain label ampoules of sterile water and saline were prepared by the Mater Health Service Pharmacy for Australian sites and the Ipswich Hospital NHS Trust Pharmacy Manufacturing Unit for the UK site. Ampoules were numbered according to a randomization schedule prepared independently and packed in opaque polyethylene bags arranged in numerical order stratified by site. Two sets of ampoules were included in each bag for use if the woman requested repeat injections. As injections of saline is perceived to be less painful than sterile water [16], the primary midwife providing care for the woman was required to be absent from the room whilst two other midwives administered the injections. This prevented the woman's primary midwife from observing her reaction to the injections and making an assumption regarding which arm of the trial the woman had been randomised to. The woman and midwives providing the injection were also instructed not to discuss the reaction to the injections administered with the primary midwife. This approach has been used in previous blinded trials [16,18]. All investigators with access to the data and involved in the data analysis were blinded to allocation until the final analysis was complete

2.3. Procedures

Women were administered 0.1–0.3 ml of either sterile water or normal saline intracutaneously into four points surrounding the Michaelis Rhomboid. Two injections were given over the posterior-superior iliac spines with the remaining two given approximately two centimetres posterior and one centimetre medial to the posterior-superior iliac spines respectively. This is a standard technique for administration and described in previous trials [16,18]. The volume injected at each site may vary depending on tissue depth and visual estimation of the size of the resulting bleb, ideally 3–4 mm in diameter. Labour and birth care was provided based on what was standard at each site, and access to pharmacological and non-pharmacological pain relief was consistent across sites. The postpartum questionnaire was completed at most sites prior to discharge or using an online version accessed via an email link.

2.4. Primary and secondary outcomes

Whilst the Cochrane review identified both the question of analgesia and birth outcomes as principal areas for investigation, we considered the possible reduction in caesarean delivery to be the most important considering the widespread concern for increasing incidence [12]. Therefore the primary outcome was the proportion of women who had a caesarean delivery in labour. Our major secondary outcome was visual analogue pain scores at 30, 60 and 90 min post administration. Other secondary outcomes were primary indication for caesarean delivery, proportion of women having an instrumental delivery, and primary indication for assisted delivery. Other labour and birth data such as foetal position and cervical dilation at randomization, induction, augmentation, duration of labour, pharmacological analgesia, incidence of postpartum haemorrhage (defined as minor: 500–999 ml and major: more than 1000 ml) [19], labour and birth complications, puerperal complications, and perineal status were recorded. Neonatal data included Apgar scores, proportion of neonates admitted to a special or intensive care nursery, and resuscitation required at birth.

2.5. Statistical analysis

The meta-analysis of SWI use in labour reported caesarean delivery rates in the SWI groups were approximately half that occurring in the controls groups. However, this included studies that were not placebo controlled and dating from 1990 when the overall caesarean delivery rate was significantly lower than currently is [11,20]. Using routinely collected data from a site recording SWI use we estimated the initial sample size based on a difference in caesarean delivery of 12·5% intervention to 17·5% control with a power of 80% and a type one error of 5%. This calculation showed that a total sample size inclusive of a 10% attrition rate of 1886 women would be sufficient. Time and financial constraints made it necessary to end the recruitment prior to reaching the required sample size for the primary outcome.

All analyses were performed on an intention-to-treat basis. Descriptive statistics are reported as proportions, median (IQR) or means (±SD) with 95% confidence (CI) intervals as appropriate. All the categorical outcomes were analysed using chi-square test or Fisher's exact test (cell value <5) to calculate p values and compare proportions between the two study groups. A student *t*-test was conducted to infer the effects between two study groups for normally distributed non-repeated continuous measurements, for non-normally distributed variables a Wilcoxon rank test was used. We modified the initial statistical analysis plan described in the published protocol, prior to unblinding of the data, to include a mixed effects model. The original protocol assumed six participating sites, however the expansion of the trial to further sites required controlling for a possible cluster effect. We used a generalized linear mixed-model repeated measures analysis to investigate the difference in mean visual-analogue scale pain score prior to randomization to those at 30, 60 and 90 min after injection. Our model is a three-level model: measurement of pain scores (level 1), nested in individual participants (level 2), nested in hospitals (level 3). Our model included both fixed factors (time, treatment, and its interaction), random intercept in participant level and hospital level, and random-efficient

component in participant level (time) and in hospital level (treatment). Hospital level random effect was not significant so the final model did not include this. Linear mixed-model estimation was carried out with the use of maximum-likelihood methods and Akaike and Bayesian information criterion was checked to choose the best model (Supplementary Data Table S1). To ensure insensitivity of the pain changes to missing data, analyses were repeated after imputation (last-observation-carried-forward) but this did not affect the findings (Supplementary Data Table S2). We undertook a number of post-hoc analysis of variables not included in the original data analysis as they were relevant to the study, such as pharmacological analgesic use (other than neuraxial), neonatal birth weight, Apgar score at five minutes and neonatal resuscitation. To account for the number of clinical outcomes and the possibility of significance occurring by chance at the $p = 0.05$ level we used the Bonferroni correction (α/k; where α is the error rate and k is the number of comparisons). Following this, the level of significance for the clinical outcomes is $p<0.001$ [21]. Treatment effects were presented as RR or mean differences with 95% CIs. All statistical analyses were performed with the use of Stata (version 14).

The study was registered at the Australian New Zealand Clinical Trials Registry (No ACTRN12611000221954).

2.6. Role of the funding source

The funders had no role in the trial design, data collection, analysis, or manuscript preparation. NL, SK and YG had full access to all the data in the study, and NL and SK had final responsibility for the decision to submit for publication.

3. Results

Between December 9, 2012, and December 15, 2017, 1166 participants were recruited to the ICARIS trial, 587 to the SWI group and 579 to the saline placebo. Seven women in the SWI group (1·1%) and 12 (2·0%) in the saline placebo were excluded from analysis as completed consent forms were not provided. Therefore 580 women in the SWI group and 567 in the saline placebo were included in the intention to treat analysis. Two women (0·3%) in the SWI group did not receive the treatment compared to four (0·7%) in the saline placebo. Nine (1·5%) women receiving SWI and seven (1·2%) who received the saline placebo did not provide pain score data. Primary outcome data could not be matched from the participating site database for eight (1·3%) in the SWI group and 10 (1·7%) in the saline placebo (Fig. 1). Baseline characteristics were similar between the two groups (Table 1). The mean (± SD) age of participants was 29·3 (4·9) and 72·1% were nulliparous. At enrolment in the trial 70·8% were in spontaneous labour, foetal position was assessed as occipito-posterior in 40·2% of women, 55·7% had a cervical dilation of four centimetres or less. The mean (± SD) visual analogue pain score for back pain was 83·4 (14·4) and 67.3% had used pharmacological analgesia prior to randomization (Table 1).

The primary outcome of caesarean section occurred in 97 (17·1%) of the 580 women assigned to SWI compared to 82 (14·8%) of the 567

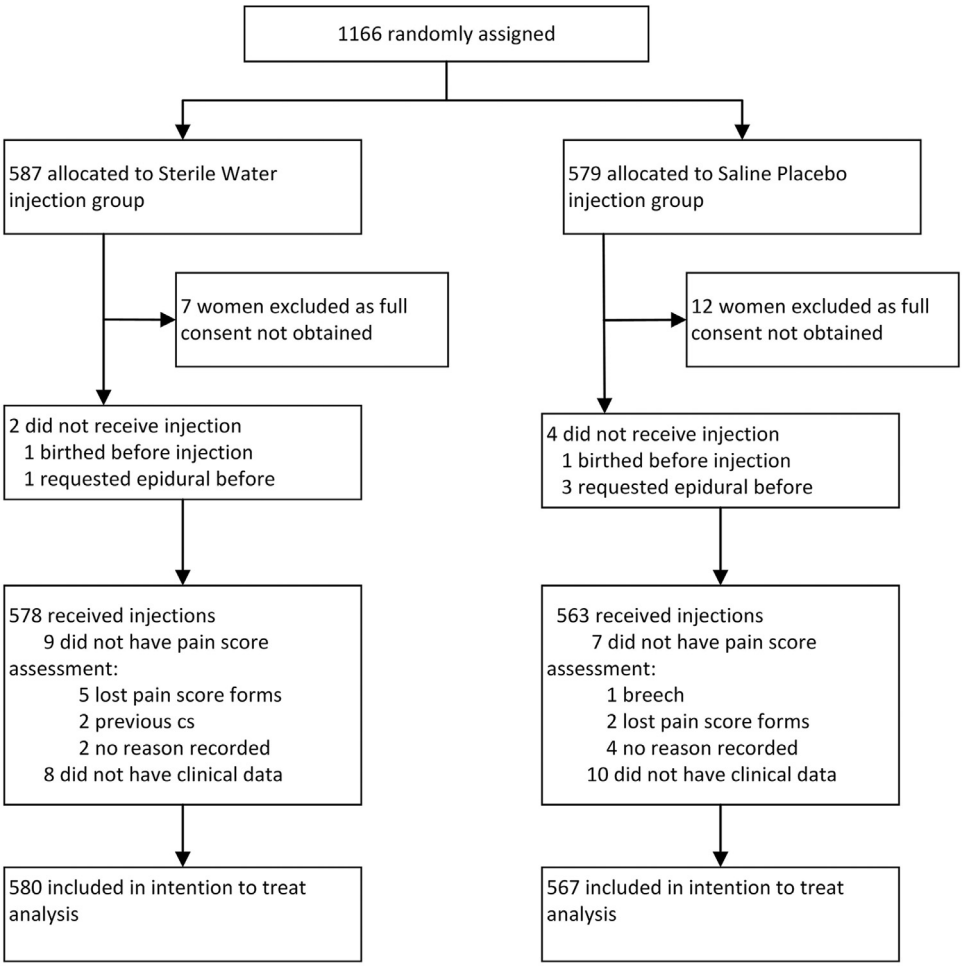

Fig. 1. Participant flow diagram.

Table 1
Characteristics of the Participants at Baseline

	Sterile Water group (n = 580)	Saline Placebo group (n = 567)
Characteristic		
Maternal Age (years)	29·5 (4·9)	29·2 (4·9)
VAS pain score prior randomization	83·3 (14·6)	83·4 (14·2)
Range	1 - 100	1 - 100
Marriage status		
Married or defacto	364 (62·8%)	343 (60·5%)
Not married or defacto	94 (16·2%)	108 (19·0%)
Not recorded	122 (21·0%)	116 (20·5%)
Parity – no.(%)		
Nulliparity	411 (70·9%)	416 (73·4%)
Multiparity	169 (29·1%)	151 (26·6%)
BMI at booking –		
Underweight BMI <18·5	14 (2·4%)	22 (3·9%)
Normal BMI 18·5 – 24·9	295 (50·9%)	293 (51·7%)
Overweight BMI 25-30	161 (27·8%)	146 (25·8%)
Obese BMI >30	92 (15·9%)	88 (15·5%)
Not recorded	18 (3·1%)	18 (3·2%)
Cervical dilation at randomization		
0-4cm	335 (57·8%)	322 (56·8%)
5-9cm	208 (35·9%)	210 (37·0%)
10cm	4 (0·7%)	8 (1·4%)
Not recorded	33 (5·7%)	27 (4·8%)
Fetal position		
OP	232 (40·0%)	229 (40·4%)
OL	144 (24·8%)	153 (27·0%)
OA	114 (19·7%)	106 (18·7%)
Undetermined	57 (9·8%)	55 (9·7%)
Not recorded	33 (5·7%)	24 (4·2%)
Analgesia used prior to randomization (multiple options)		
Nitrous oxide gas	315 (54·3%)	321 (56·6%)
None	181 (31·2%)	170 (30·0%)
Oral analgesia	76 (13·1%)	88 (15·5%)
IM/IV narcotics	75 (12·9%)	62 (10·9%)
Onset of labour		
Spontaneous	413 (71·2%)	399 (70·4%)
Induced	159 (27·4%)	158 (27·9%)
Not recorded	8 (1·4%)	10 (1·8%)

Notes: Numbers are mean (SD) or n(%)

women who received the saline placebo (RR 1·16, 95% CI 0·88–1·51; p = 0·293). The overall rate of caesarean delivery for both groups was 15·3%. Considering that recruitment ceased prior to achieving the required sample size with an actual study power of 66% based on the number of participants recruited we undertook a futility analysis to determine the likelihood that full recruitment would have changed the results of the primary outcome (analysed using PASS2019, V19·0·3) [22,23]. The results indicated that the conditional power based on the actual primary outcome (caesarean section rate of 17·1% in control vs 14·8% in intervention) was extremely small (0·5%) and the Futility Index was 99·5%. This suggests that the primary outcome was not likely to reach statistical significance of a 5% reduction had the trial continued to the planned end. Six participants were known not to have received the allocated treatment and it can be assumed that the 16 not providing pains scores may also have not received the intervention or placebo as intended. We did conduct a post-hoc per-protocol analysis for the primary outcome excluding the 22 protocol violations (intervention n = 569; placebo n = 556), the difference in rates of caesarean section remained non-significant (RR 1.14, 95%CI 0.87–1.50; p = 0.347) (Supplementary Data Table S4).

There was also no difference in rates of spontaneous (RR 0·94, 95%CI 0·86–1·04; p = 0·221) or instrumental births (RR 1·06, 95% CI 1·06 0·85–1·31; p = 617). There was no difference in other secondary labour and birth complications (Table 2). Neonatal outcomes including Apgar score, neonatal resuscitation and admission to special care nurseries were not significantly different (Table 3). No adverse events related to injections of either sterile water or normal saline were noted during the trial.

Prior to treatment the VAS scores (100 mm scale) for back pain between groups were 83.4 (SWI) versus 83.5 (placebo) (mean difference 0.1, 95% CI −2·3–2·2; p = 0.954). At 30 min following treatment 330 (60·8%) of 543 women in the SWI group compared to 163 (31·4%) of 520 women in the saline placebo group reported a 30% reduction in VAS scores (RR 1·94, 95% CI 1·68–2·24; p=<0·001). In the SWI group 235 (43·3%) of 543 women reported an at least 50% reduction in VAS scores at 30 min post injection compared to 94 (18·1%) of 520 women receiving the saline placebo (RR 2·39, 95% CI 2·39 1·95–2·94; p=<0·001). This difference in pain score reduction remained significant at 60 and 90 min (Table 2). Whilst women may use multiple combinations of pharmacological and neuraxial analgesic during labour, the overall use of conventionally available analgesia after randomization did not differ significantly between groups (Table 2). Nitrous oxide inhalation was used by 386 (66·6%) of 580 women in the SWI group and 383 (67·6%) of 567 in the saline placebo group (RR 0·99, 95% CI 0·91–1·07; p = 0·720). In the SWI group epidurals were used by 215 (37·1%) of 580 compared to 221 (39·0%) of women receiving the saline placebo (RR 0·95, 95% CI 0·82–1·10; p = 0·506).

Maternal satisfaction with analgesic effect of SWI was assessed in four domains. Surveys were returned by 70% (407/580) of women in the SWI group and 71% (403/567) of the placebo group. More women in the SWI group than the saline placebo group replied positively regarding their experience of effectiveness in reliving back pain (p=<0·001); overall satisfaction with the treatment (p = 0·001); would choose the treatment in a subsequent pregnancy (p = 0·05); and would recommend the treatment to other women (p = 0·001) (Table 4).

4. Discussion

In this randomised trial involving women in labour experiencing severe back pain, we did not find a significant difference in the rate of caesarean delivery between participants randomised to either sterile water or saline placebo injections. For our main secondary outcome of pain relief, the trial did demonstrate that significantly more women receiving SWI reported an at least 30% or at least 50% reduction in self assessed back pain at 30, 60 and 90 min post treatment when compared with the control. There were no adverse events associated with either SWI or the placebo.

The null results for the primary outcome of caesarean delivery contradict the findings of the meta-analysis conducted by Hutton et al. [11] and support those of the Cochrane review conducted by Derry et al. [6]. The meta-analysis by Hutton et al. included two trials that were not placebo controlled, comparing water injections to acupuncture [24], transcutaneous nerve stimulation or massage, water immersion and mobility in labour [25], whereas Derry et al. included only placebo controlled trials [6]. Both reviews described significant levels of heterogeneity which may also account for the conflicting results. The sample size in our trial (n = 1166) was larger than the pooled data available in either Hutton et al. (n = 828) or Derry et al. (n = 766). Whilst not directly comparable the overall caesarean delivery rate in our trial (15.6%) was within the range for in-labour rates reported in the UK (14·2%) and the state that contributed most of the Australian participants (17·0%) [26,27].

For the main secondary outcome of analgesic effect, women were twice as likely to report an at least 30% or 50% reduction in back pain following water injections compared to the placebo during the 90 min data collection period. Only one previous trial on the use of water injections reported in this dichotomous format and whilst the results also suggested a significant analgesic effect from the procedure, the study was not a placebo controlled superiority trial, rather a non-inferiority design comparing analgesia outcomes from either a

Table 2
Primary and Secondary Maternal Outcomes

	Sterile Water group (N=580)	Saline Placebo group (N-567)	Estimates (95% CI)	P-value
Primary outcome				
Caesarean section	97 (17·1%)	82 (14·8%)	1·16 (0·88, 1·51)[#]	0·293
Secondary outcomes				
Spontaneous vaginal birth	339 (59·6%)	351 (63·1%)	0·94 (0·86, 1·04)[#]	0·221
Instrumental vaginal birth	133 (23·4%)	123 (22·1%)	1·06 (0·85, 1·31)[#]	0·617
Missing	11	11		
VAS pain score prior to injection			-0·1 (1·1) (-2·3, 2·2)[*]	0·954
Mean (SD)	83·4 (0·8)	83·5 (0·8)		
Range	0-100	0-100		
VAS pain score reduced at least 30% at 30 minutes			1·94 (1·68 to 2·24)[#]	<0·001
Yes	330 (60·8%))	163 (31·4%)	..	
No	213 (39·2%)	357 (68·6%)	..	
Missing	37	47	..	
VAS pain score reduced at least 30% at 60 minutes			1·78 (1·51 to 2·11)[#]	<0·001
Yes	241 (53·3%)	128 (29·9%)	..	
No	211 (46·7%)	300 (70·1%)	..	
Missing	128	139	..	
VAS pain score reduced at least 30% at 90 minutes			1·81 (1·46 to 2·23)[#]	<0·001
Yes	171 (46·0%)	88 (25·4%)	..	
No	201 (54·0%)	258 (74·6%)	..	
Missing	208	221	..	
VAS pain score reduced at least 50% at 30 minutes			2·39 (1·95 to 2·94)[#]	<0·001
Yes	235 (43·3%)	94 (18·1%)	..	
No	308 (56·7%)	426 (81·9%)	..	
Missing	37	47	..	
VAS pain score reduced at least 50% at 60 minutes			1·84 (1·47 to 2·30)[#]	<0·001
Yes	165 (36·5%)	85 (19·9%)	..	
No	287 (63·5%)	343 (80·1%)	..	
Missing	128	139	..	
VAS pain score reduced at least 50% at 90 minutes			1·97 (1·50 to 2·59)[#]	<0·001
Yes	125 (33·6%)	59 (17·1%)	..	
No	247 (66·4%)	287 (82·9%)	..	
Missing	208	221	..	
Duration of first stage of labour			..	0·575
Minutes	435 (240-630)	412 (245-600)	..	
Missing	53	56	..	
Duration of second stage of labour after vaginal births			..	0·844[¶]
Minutes	60 (23-117)	52 (22-117)	..	
Missing	7	8	..	
Augmentation from spontaneous labour			0·99 (0·85 to 1·15)[#]	0·865
Yes	188 (45·5%)	184 (46·1%)	..	
No	225 (54·5%)	215 (53·9%)	..	
Nitrous oxide gas used in labour			0·99 (0·91 to 1·07)[#]	0·720
Yes	386 (66·6%)	383 (67·6%)	..	
No	194 (33·4%)	184 (32·4%)	..	
Epidural used in labour			0·95 (0·82 to 1·10)[#]	0·506
Yes	215 (37·1%)	221 (39·0%)	..	
No	365 (62·9%)	346 (61·0%)	..	
IM/IV narcotics used in labour			1·02 (0·79 to 1·31)[#]	0·893
Yes	102 (17·6%)	98 (17·3%)	..	
No	478 (82·4%)	469 (82·7%)	..	
Cervical dilation prior Caesarean section			1·08 (0·55 to 2·10)[#]	0·820
3cm or less	16 (17·8%)	13 (16·5%)	..	
More than 3cm	74 (82·2%)	66 (83·5%)	..	
Missing	7	3	..	
Reasons for Caesarean section (multiple options)			..	
Prolonged labour	72 (74·2%)	65 (79·3%)	..	0·428
Fetal distress	30 (30·9%)	21 (25·6%)	..	0·432
Failed instrumental births	7 (7·2%)	6 (7·3%)	..	0·979
Other: malposition	10 (10·3%)	7 (8·5%)	..	0·687
Missing	3	1	..	

Notes: Data are n(%) or Median(IQR). VAS = visual analogue scale. VAS pain scores range 0-100 where 0 = no pain and 100 = worst pain imaginable. IM = intramuscular. IV = Intravenous.

[#] Relative Risk (RR).

[*] Mean difference (95% CI).

[¶] Wilcoxon rank test for median p value . Reference group for caesarean section is inclusive of spontaneous vaginal birth, instrumental birth and missing data. Reference group for Spontaneous vaginal birth is inclusive on Caesarean Section, Instrumental birth and missing data. Reference group for Instrumental birth is inclusive of Caesarean Section, Spontaneous vaginal birth and missing data.

single or four injection techniques [18]. Other than the transient pain associated with injections of sterile water, no adverse effects of the procedure have been reported in this or previous trials underpinning the safety of the procedure. Women who received water injections reported higher levels of satisfaction and this is consistent with previous studies [18,28].

Table 3
Secondary Neonatal Outcomes

	Sterile Water group (N=580)	Saline Placebo group (N-567)	Estimates (95% CI)	P-value
Birthweight			-4·6 (-56·71 to 47·56)*	0·863
Grams	3510·6 (441·3)	3515·2 (449·1)	..	
Missing	14	10	..	
Apgar score at 5 minutes			2·06 (0·94, 4·50)#	0·072
<7	19 (3·3%)	9 (1·6%)	..	
≥7	553 (96·7%)	548 (98·4%)	..	
Missing	8	10	..	
Resuscitation needed at birth	1·01 (0·77 to 1·31)#	0·963		
No	479 (83·7%)	467 (83·8%)	..	
Yes	93 (16·3%)	90 (16·2%)	..	
Not recorded	8	10	..	
Resuscitation methods used				
Suction (oral, pharyngeal etc)	61 (10·5%)	52 (9·2%)	..	0·661
Bag and mask	47 (8·1%)	42 (7·4%)	..	0·798
Facial oxygen	18 (3·1%)	16 (2·8%)	..	0·841
Suction of meconium via ETT	5 (0·9%)	6 (1·1%)	..	0·821
IPPV via ETT	2 (0·3%)	4 (0·7%)	..	0·607¶
External cardiac massage	3 (0·5%)	0 (0·0%)	..	0·251¶
Drug	1 (0·2%)	0 (0·0%)	..	0·642¶
Admission to SCN			1·34 (0·89 to 2·02)#	0·156
No	521 (91·1%)	520 (93·4%)	..	
Yes	51 (8·9%)	37 (6·6%)	..	
Missing	8	10	..	
Admission to ICN			1·54 (0·76 to 3·15)#	0·424
No	553 (96·7%)	545 (97·8%)	..	
Yes	19 (3·3%)	12 (2·2%)	..	
Missing	8	10	..	

Notes Data are n(%) or mean(SD).
Relative Risk (RR).
* Mean difference (95% CI).
¶ Fisher's exact p value presented when the expected value of a cell<5. ETT = endotracheal tube, IPPV = intermittent positive pressure ventilation, SCN = special care nursery, ICN = intensive care nursery

Table 4
Maternal Satisfaction

	Sterile Water (n=407)	Placebo (n=403)	p-value
How effective the injections relieving your back pain			
Very effective	145 (36·4%)	56 (14·4%)	<0·001
Rather effective	121 (30·4%)	104 (26·8%)	
Not very effective	81 (20·4%)	107 (27·6%)	
Not effective at all	51 (12·8%)	121 (31·2%)	
Not recorded	9 (2·2%)	15 (3·7%)	
Overall satisfaction with the treatment			<0·001
Very satisfied	134 (33·8%)	64 (16·5%)	
Satisfied	143 (36·0%)	134 (34·5%)	
Dissatisfied	77 (19·4%)	134 (34·5%)	
Very dissatisfied	43 (10·8%)	56 (14·4%)	
Not recorded	10 (2·4%)	15 (3·7%)	
Choose the same treatment again			0·050
Yes	237 (60·3%)	207 (53·3%)	
No	156 (39·7%)	181 (46·7%)	
Not recorded	14 (3·4%)	15 (3·7%)	
Recommend the treatment to other women			0·001
Yes	283 (71·8%)	238 (61·0%)	
No	111 (28·2%)	152 (39·0%)	
Not recorded	13 (3·1%)	13 (3·2%)	

Notes: Data are n (%)

In this trial we chose a pragmatic design to explore any relationship between water injections and the use of other more standard pharmacological options, in particular neuraxial analgesia such as epidurals. The trial results indicated that there was no difference between groups in the use of epidurals, or any other pharmacological forms of analgesia during labour (nitrous oxide, narcotics). This is similar to results noted in previous SWI trials [6]. We were not able to record the time duration between the administration of the injections and epidural as insertion may occur at any point during labour and this information was not documented consistently or part of perinatal data routinely collected at participating sites. It is not unusual for women to use a number of different forms of analgesia during labour as the intensity and location of pain may alter as labour progresses [29]. The analgesic effects of counter-irritation agents, such as SWI, have been demonstrated as being most effective in the area they are administered [30]. Therefore, SWI administered in the lumbar region may have no effect on the uterine pain normally associated with labour, which may become more pronounced once the back pain has been relieved. Other analgesics routinely used during labour, such as nitrous oxide inhalation, have also been shown not to have any impact on epidural use or mode of birth [31]. Interestingly, more than half of the women in our study had used nitrous oxide and/or narcotics prior to randomisation, suggesting that these pharmacological approaches were judged inadequate by women to manage the back pain that they were experiencing. In a prospective comparison of epidural block, para-cervical block, pethidine, nitrous oxide inhalation, and water injections, more women receiving water injections rated the analgesic effect on overall labour pain experience as good or moderate compared to those using pethidine or nitrous oxide [32]. Randomised trials have also demonstrated the superiority of water injections for relieving back pain in labour compared to transcutaneous electric nerve stimulation, combinations of water immersion, massage and mobilization [25] and acupuncture [24].

A number of studies have described considerable variation between countries in the use of water injections as a method of relieving back pain in labour, and have highlighted high degrees of scepticism amongst clinicians regarding the procedure [8,9]. This may reflect the impact of national guidelines that do not support the use of SWI based on concerns regarding evidence for safety, effectiveness, effect on birth outcomes, and acceptability by women [7]. The

results of this trial largely address those concerns and have demonstrated the effectiveness of water injections to relieve back pain in labour for the majority of women.

This trial is larger than all previous trials comparing SWI to a placebo, and as such is able to detect differences with greater confidence. The trial was undertaken at sites that offered ethnic and socio-economic diversity contributing to the generalisability of the findings. Interpretation of the null results in relation to mode of birth and other forms of pain relief is challenging. It is clear that SWIs were more effective than placebo for relieving back pain up to 90 min post administration, and more women were very satisfied with SWI compared to placebo. However, it would not be expected to impact abdominal pain in labour which may be driving these results. It is interesting to note the analgesic effect from the normal saline placebo and that a similar proportion of women would request the treatment again: SWI (60.3%) versus normal saline (53.3%) p = 0.05 and although lower than SWI, >60% of women receiving the placebo would recommend it to others. Normal saline for injection is considered an active placebo in that it mimics the effects of the intervention as participants experience both some degree of injection discomfort and a mild analgesic effect. This can reduce bias in placebo controlled trials by blinding participants but may also have impacted findings due to the pain relief provided by the injections of normal saline [33,34].

This trial has some notable limitations. Firstly, the original sample size was not achieved within the study timeframe however a futility analysis indicates that it is unlikely the results would have changed if full recruitment had been achieved. Nonetheless, based on previous studies, the trial is powered *a priori* for the main secondary outcome of pain relief [16,28,35]. Furthermore we adjusted the level of significance to account for multiple clinical outcomes. Some VAS data were incomplete, however this was mostly due to women progressing to birth or insertion of an epidural. Whilst our study was conducted in countries where women have access to a range of pharmacological and non-pharmacological options, it is likely that this simple, safe and effective method of analgesia for back pain in labour would work in any setting where the carer has been trained in its administration. The exclusion of women utilising private insurance may reflect a limitation of the generalisability of the effect on birth outcomes but this is not likely to impact on analgesic response. Furthermore, we only investigated the analgesic effect of the procedure on back pain and cannot report treatment effect on other forms of labour-related pain. Data for non-pharmacological analgesia and breast-feeding at discharge was not available from all sites therefore this data was not analysed as per the study protocol. The effect of SWI on health costs, and women's perception of relaxation and birth experience will need to be evaluated in further analysis.

In conclusion, our trial did not demonstrate any effect of the use of SWI on rates of caesarean delivery or other birth outcomes. Whilst a secondary outcome and subject to correction for multiple testing, the study did provide evidence, in a clinically relevant format, for the analgesic efficacy and safety of water injections for back pain in labour. This outcome has implications for the procedure across a diverse range of health settings worldwide. The procedure is inexpensive in terms of resources with a level of technical skill that requires minimal training. In scenarios where use of epidurals to manage back pain is either unwanted by labouring women, as in birth centres or homebirth, or unavailable such as in remote or developing health structures, the use of water injections presents an effective and safe alternative. The wider acceptance and use of water injections as an analgesic would assist in addressing the need for pain relief strategies with few side effects and future research should focus on use for generalised labour pain, and other acute and chronic pain syndromes.

Declaration of Competing Interest

We declare no competing interests.

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Data sharing

De-identified individual participant data that underlie the results reported in this article (text, tables, figures, and appendices) will be made available along with the study protocol. Data will be available beginning 9 months after publication of the Article to researchers whose proposed use of the data is approved by NL, SK and YG. Proposals should be directed to the corresponding authors and requesters will need to sign a data access agreement.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100447.

References

[1] Melzack R, Schaffeberg D. Low-back pain during labour. Am J Obstet Gynecol 1987;158:901–5.
[2] Rogers Jr RM. Basic neuroanatomy for understanding pelvic pain. J Am Assoc Gynecol Laparosc 1999;6(1):17–25.
[3] Mårtensson LB, Hutton EK, Lee N, Kildea S, Gao Y, Bergh I. Sterile water injections for childbirth pain: an evidenced based guide to practice. Women Birth 2018;31(5):380–5.
[4] Melzack R, Wall P. Pain mechanisms: a new theory. Science 1965;150(699):971–9.
[5] Le Bars D, Dickenson AH, Besson J-m. Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. Pain 1979;6(3):305–27.
[6] Derry S, Straube S, Moore RA, Hancock H, Collins SL. Intracutaneous or subcutaneous sterile water injection compared with blinded controls for pain management in labour. Cochrane Datab Syst Rev 2012;1:CD009107. doi: 10.1002/14651858.CD009107.pub2.
[7] National Institute for Health and Care Excellence. Intrapartum care: care of healthy women and their babies during childbirth (CG190). 2014. http://www.nice.org.uk/guidance/cg190/resources.
[8] Lee N, Martensson LB, Kildea S. Cross sectional study of Australian midwives knowledge and use of sterile water injections for pain relief in labour. Women Birth 2012;25(4):e74–e9.
[9] Lee N, Jomeen J, Mårtensson LB, Emery V, Kildea S. Knowledge and use of sterile water injections amongst midwives in the United Kingdom: a cross-sectional study. Midwifery 2019;68:9–14.
[10] Simpson CN, Chambers CN, Sharshiner R, Caughey AB. Effects of persistent occiput posterior position on mode of delivery [256]. Obstetr Gynecol 2015;125:82S–3S.
[11] Hutton EK, Kasperink M, Rutten M, Reitsma A, Wainman B. Sterile water injection for labour pain: a systematic review and meta-analysis of randomised controlled trials. BJOG 2009;116(9):1158–66.
[12] Betrán AP, Temmerman M, Kingdon C, et al. Interventions to reduce unnecessary caesarean sections in healthy women and babies. The Lancet 2018;392(10155):1358–68.
[13] Lee N, Mårtensson LB, Homer C, et al. Impact on Caesarean section rates following injections of sterile water (ICARIS): a multicentre randomised controlled trial. BMC Pregnancy Childbirth 2013;13(1):105.
[14] Collins S, Moore R, McQuay H. The visual analogue pain intensity scale: what is moderate pain in millimetres. Pain 1997;72:95–7.
[15] Einarsdóttir K, Kemp A, Haggar FA, et al. Increase in caesarean deliveries after the Australian private health insurance incentive policy reforms. PLoS One 2012;7(7):e41436.

[16] Mårtensson L, Wallin G. Labour pain treated with cutaneous injections of sterile water: a randomised controlled trial. BJOG Int J Obstetr Gynaecol 1999;106(7):633–7.
[17] Saxena K, Nischal H, Batra S. Intracutaneous injections of sterile water over the sacrum for labour analgesia. Indian J Anaesth 2009;53(2):169–73.
[18] Lee N, Webster J, Beckmann M, et al. Comparison of a single vs. a four intradermal sterile water injection for relief of lower back pain for women in labour: a randomised controlled trial. Midwifery 2013;29(6):585–91.
[19] Kerr R, Weeks A. Postpartum haemorrhage: a single definition is no longer enough. BJOG Int J Obstetr Gynaecol 2017;124(5):723–6.
[20] Hehir MP, Ananth CV, Siddiq Z, Flood K, Friedman AM, D'Alton ME. Cesarean delivery in the United States 2005 through 2014: a population-based analysis using the Robson 10-Group Classification System. Am J Obstet Gynecol 2018;219(1) 105.e1-.e11.
[21] McDonald JH. Handbook of biological statistics. Baltimore, MD: Sparky House publishing; 2009.
[22] Snapinn S, Chen MG, Jiang Q, Koutsoukos T. Assessment of futility in clinical trials. Pharmaceut Stat J Appl State Pharmaceut Ind 2006;5(4):273–81.
[23] Sully BG, Julious SA, Nicholl J. An investigation of the impact of futility analysis in publicly funded trials. Trials 2014;15(1):61.
[24] Martensson L, Stener-Victorin E, Wallin G. Acupuncture versus subcutaneous injections of sterile water as treatment for labour pain. Acta Obstet Gynecol Scand 2008;87(2):171–7.
[25] Labrecque M, Nouwen A, Bergeron M, Rancourt JF. A randomized controlled trial of nonpharmacologic approaches for relief of low back pain during labor. J Fam Pract 1999;48(4):259–63.
[26] NMPA Project Team. National Maternity and Perinatal Audit: Clinical Report 2017 RCOG London. 2017.
[27] Pregnancy Outcome Unit, Prevention and Population Health Branch. Pregnancy outcome in South Australia 2016. SA Health; 2018 Govt. of South Australia.
[28] Trolle B, Moller M, Kronborg H, Thomsen S. The effect of sterile water blocks on low back labor pain. Am J Obstetr Gynecol 1991;164(5 Pt 1):1277–81.
[29] Lowe NK. The nature of labor pain. Am J Obstet Gynecol 2002;186(5, Suppl):S16–24.
[30] Gammon D., Starr I.Studies on the relief of pain by counterirritation. 1940.
[31] Sutton CD, Butwick AJ, Riley ET, Carvalho B. Nitrous oxide for labor analgesia: utilization and predictors of conversion to neuraxial analgesia. J Clin Anesth 2017;40:40–5.
[32] Ranta P, Jouppila P, Spalding M, Kangas-Saarela T, Hollmén A, Jouppila R. Parturients' assessment of water blocks, pethidine, nitrous oxide, paracervical and epidural blocks in labour. Int J Obstet Anesth 1994;3(4):193–8.
[33] Jensen JS, Bielefeldt AØ, Hróbjartsson A. Active placebo control groups of pharmacological interventions were rarely used but merited serious consideration: a methodological overview. J Clin Epidemiol 2017;87:35–46.
[34] Rief W, Glombiewski JA. The hidden effects of blinded, placebo-controlled randomized trials: an experimental investigation. PAIN® 2012;153(12):2473–7.
[35] Bahasadri S, Ahmadi-Abhari S, Dehghani-Nik M, Habibi GR. Subcutaneous sterile water injection for labour pain: a randomised controlled trial. Aust N Z J Obstetr Gynaecol 2006;46(2):102–6.