Closed incision negative pressure wound therapy versus standard dressings in obese women undergoing caesarean section: multicentre parallel group randomised controlled trial

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ABSTRACT

OBJECTIVE

To determine the effectiveness of closed incision negative pressure wound therapy (NPWT) compared with standard dressings in preventing surgical site infection (SSI) in obese women undergoing caesarean section.

DESIGN

Multicentre, pragmatic, randomised, controlled, parallel group, superiority trial.

SETTING

Four Australian tertiary hospitals between October 2015 and November 2019.

PARTICIPANTS

Eligible women had a pre-pregnancy body mass index of 30 or greater and gave birth by elective or semi-urgent caesarean section.

INTERVENTION

2035 consenting women were randomised before the caesarean procedure to closed incision NPWT (n=1017) or standard dressing (n=1018). Allocation was concealed until skin closure.

MAIN OUTCOME MEASURES

The primary outcome was cumulative incidence of SSI. Secondary outcomes included depth of SSI (superficial, deep, or organ/body space), rates of wound complications (dehiscence, haematoma, seroma, bleeding, bruising), length of stay in hospital, and rates of dressing related adverse events. Women and clinicians were not masked, but the outcome assessors and statistician were blinded to treatment allocation. The pre-specified primary intention to treat analysis was based on a conservative assumption of no SSI for a minority of women (n=28) with missing outcome data. Post hoc sensitivity analyses included best case analysis and complete case analysis.

RESULTS

In the primary intention to treat analysis, SSI occurred in 75 (7.4%) women treated with closed incision NPWT and in 99 (9.7%) women with a standard dressing (risk ratio 0.76, 95% confidence interval 0.57 to 1.01; P=0.06). Post hoc sensitivity analyses to explore the effect of missing data found the same direction of effect (closed incision NPWT reducing SSI), with statistical significance. Blistering occurred in 40/996 (4.0%) women who received closed incision NPWT and in 23/983 (2.3%) who received the standard dressing (risk ratio 1.72, 1.04 to 2.85; P=0.03).

CONCLUSION

Prophylactic closed incision NPWT for obese women after caesarean section resulted in a 24% reduction in the risk of SSI (3% reduction in absolute risk) compared with standard dressings. This difference was close to statistical significance, but it likely underestimates the effectiveness of closed incision NPWT in this population. The results of the conservative primary analysis, multivariable adjusted model, and post hoc sensitivity analysis need to be considered alongside the growing body of evidence of the benefit of closed incision NPWT and given the number of obese women undergoing caesarean section globally. The decision to use closed incision NPWT must also be weighed against the increases in skin blistering and economic considerations and should be based on shared decision making with patients.

TRIAL REGISTRATION

ANZCTR identifier 12615000286549.

WHAT IS ALREADY KNOWN ON THIS TOPIC

A 2014 Cochrane systematic review compared closed incision negative pressure wound therapy (NPWT) with a standard dressing for surgical site infection (SSI), wound complications, and time to healing

Evidence for the effect of closed incision NPWT in preventing SSI and wound complications was unclear, and the overall quality of the evidence was low

A more recent meta-analysis including seven studies reported inconclusive evidence of the effectiveness closed incision NPWT for obese women giving birth by caesarean section

WHAT THIS STUDY ADDS

The results of this large trial add to the body of evidence in published systematic reviews suggesting that prophylactic closed incision NPWT may be effective in reducing SSI rates

The use of prophylactic closed incision NPWT for obese women undergoing caesarean section was associated with a small but significant increase in skin blistering

The use of closed incision NPWT in obese women undergoing caesarean section needs to be considered alongside the risk of blistering and cost effectiveness

Introduction

The use of caesarean section in birthing women varies widely, with Nordic countries reporting low rates and other Western countries such as Australia, Canada, the UK, and the US reporting higher rates (15-17% *v* 25-32%).[1] Compared with vaginal birth, caesarean section is associated with increased morbidity and mortality.[2] The World Health Organization defines people as obese

if their body mass index is greater than or equal to 30.0.[1] Obesity in pregnancy is increasingly common; in Australia, more than 50% of women are overweight or obese on entering pregnancy.[1] Postoperative wound complications such as surgical site infection (SSI), dehiscence (splitting open of a surgically closed wound), and formation of haematoma and seroma are common complications of surgical procedures,[3] particularly among women with obesity, diabetes, or both.[4] SSI is an important global concern that can contribute to re-intervention and treatment, increased length of stay in hospital, delayed wound healing, and, in some cases, death.[5 6] Maternal obesity increases the woman's risk of developing SSI and other wound complications threefold, which delays recovery, increases discomfort, and reduces quality of life.[4 7]

Over the past decade, the use of single use closed incision negative pressure wound therapy (NPWT) dressings in high risk surgical incisions has been increasing, with the aim of reducing the risk of SSI and other associated wound complications.[8] Closed incision NPWT is a sealed non-invasive system that applies suction (negative pressure) on the wound site that has been closed, for example, by sutures, staples, or glue. The surgical incision is covered with semi-occlusive adhesive dressing connected by tubing to a suction pump.[9] The suction pump exerts negative pressure to the closed incision and removes wound fluid with recommended pressures usually between −50 mm Hg and −125 mm Hg,[10] depending on the manufacturer's instructions.[11] The mechanism of action is unclear but is purported to include reduced bacterial entry into the wound while removing blood and exudate and stimulating granulation.

In 2010-11, two simplified NPWT devices became commercially available (Prevena (KCI) and PICO (Smith & Nephew)). A Cochrane review published before we started this trial and its subsequent update found only low quality evidence in any population, with most studies sponsored by industry.[8 12] Meta-analytic results of the updated Cochrane review reported inconclusive evidence of the effectiveness of closed incision NPWT specifically for obese women undergoing caesarean section (seven studies).[8] At the time we began our research, all other trials in this population were small, single site, and industry funded. In this study, we aimed to compare the effectiveness and safety of prophylactic closed incision NPWT and standard surgical dressings on the cumulative incidence of SSI in obese women undergoing elective and semi-urgent caesarean section.

Methods

Study design and participants

We conducted a pragmatic, randomised, controlled, parallel group, superiority trial in four large public hospitals in southeast Queensland, Australia. We made no changes to the methods after the start of the trial. We identified potentially eligible women at their routine 36 week antenatal visit. Research nurses at each site screened women in antenatal clinics, antenatal wards, and birthing suites. Women were eligible if they were booked for elective (category 4) or semi-urgent (categories 2-3) caesarean section,[13] recorded a pre-pregnancy body mass index of 30 or higher, and were able to provide written informed consent. We excluded women who needed an urgent caesarean section (category 1), had an infection in hospital including during labour or immediately before caesarean section, had participated in the trial in a previous pregnancy, or were unable to speak or understand English with no interpreter present. Written informed consent was obtained from all participants. The protocol has been published.[14]

Randomisation and masking

We used a web based central randomisation service to randomly assigned eligible, consenting women (1:1) just before the caesarean procedure to receive either a closed incision NPWT dressing or the standard hospital dressing. To ensure that equal numbers of participants were assigned to each group, we used random block sizes of four, six, and eight, stratified by hospital. Allocation was concealed until after skin closure. The nature of the intervention meant that women, clinical staff, and research staff were not blinded to treatment after allocation. Data were reviewed by two independent, blinded outcome assessors to determine primary and secondary wound endpoints, and discrepancies were adjudicated by a third blinded assessor. Principal investigators, including the trial statistician, were also blinded to group allocation. The clinical trial coordinator trained and supervised research nurses and audited the quality of data and compliance of randomisation.

Procedures

All women received standard care, according to local hospital and national health department guidelines.[15] Before the skin incision, the woman's abdomen was prepared with either alcoholic or aqueous chlorhexidine or betadine. All women received a lower transverse suprapubic skin incision, and two obstetricians, usually a trainee registrar supervised by a consultant, carried out the operation. The method of skin closure (suture or staples) was based on the obstetrician's preference. The operating obstetrician (or delegate) applied the closed incision NPWT and standard dressings under sterile conditions in the operating room immediately after skin closure. Women assigned to the closed incision NPWT group received a PICO dressing (Smith & Nephew, Hull, UK), which was left intact for approximately five to seven days as recommended by the manufacturer. This particular NPWT product was used in two earlier pilot studies.[16 17] The PICO product (size 10×30 cm or 10×40 cm) has a small discrete pump powered by two AA lithium batteries with an absorbent polyurethane foam dressing that holds wound exudate away from the skin. A tube is inserted into the foam, and a continuous negative pressure of 80 mm Hg is applied after application of the dressing. The PICO dressing was reinforced around

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each of the four edges with four pieces of adhesive tape included in the dressing kit, as per the manufacturer's instructions. All clinical staff providing care received ongoing training and support in the correct application and use of the PICO dressings, as well as monitoring dressing changes and completing documentation daily for assessment of protocol fidelity.

The control group comprised women allocated to the standard hospital dressing. The choice of standard dressings was based on the treating obstetrician's usual choice of dressing (for example, hydrocolloid or transparent), applied according to the manufacturer's recommendations after skin closure in the operating room. Across all hospital sites, the standard dressing was left intact for five to seven days.

We collected clinical data from several sources, including electronic records, direct observation, and self-reporting by women during hospital admission and after discharge. Demographic data (pre-pregnancy body mass index, parity/gravidity, comorbidities, measurement of health status (Health Related Quality of Life Short Form Survey SF-12 v-2) were obtained on enrolment; surgical data (American Society of Anaesthesiologists category, type of anaesthetic, antibiotic administration, hair removal method, surgical approach, wound closure layers, suture materials, length of operation) were obtained on the day of the caesarean section. Research nurses visited women on postoperative day 2 and collected vital signs, SSI related data using a structured tool based on the Centres of Healthcare Related Infection Surveillance and Prevention guidelines identifying signs and symptoms of SSI (that is, redness, swelling, pain/tenderness, watery or purulent discharge),[18] pain associated with the dressing, and women's satisfaction with the NPWT dressing. After discharge from hospital, research nurses conducted telephone interviews with all women weekly (from the day of their surgery) until 28 days after discharge. They asked women a series of questions about SSI symptoms, SF-12 v2, and related resource use including health professional visits. On day 30, research nurses audited all participants' hospital electronic health records to check for documented evidence of SSI and wound complications (chart data documented wound complications, reoperations and hospital readmission due to wound complications, use of antibiotics for wound complications, type of SSI, signs and symptoms of SSI).

Outcome assessors were blinded to group allocation, the intervention and its comparator, and study hypotheses. These assessors were experienced registered nurses and performed outcome assessment of primary (SSI) and secondary wound related outcomes (SSI type, wound complications) for all women enrolled in the study. Each outcome assessor independently ascertained wound outcomes, and regular inter-rater consistency checks were undertaken throughout the trial. Where discrepancies in assessment of signs and symptoms existed, a third outcome assessor (nurse practitioner in wound care) adjudicated decisions. We defined loss to follow-up as lacking both 30 day medical record data and follow-up phone interview data over the four weekly time points on the primary outcome (SSI). Thus, a woman might be missing up to three interviews but would not be considered lost to follow-up unless her 30 day chart was also missing. Each week, nurses attempted to contact women or their contact person up to three times. Therefore, for all women who were not lost to follow-up and did not withdraw their participation after randomisation, we had data on primary outcome, SSI type (where SSI occurred), and wound complications.

All data were entered directly into secure portable tablets using a purpose built research data capture (REDCap) database and form based interface. Research nurses had access to the data at their hospital site only, and clinical staff did not have access to research data. The clinical trial coordinator audited the quality and completeness of data and adherence to the protocol, as well as visiting sites for training and monitoring.

Outcomes

The primary outcome was the cumulative incidence of SSI at 30 days after surgery, as defined by Centers for Disease Control and Prevention (CDC) guidelines. Secondary clinical outcomes included type of SSI (superficial, deep, or organ/body space),[18] any type of wound complication (dehiscence, haematoma, seroma, bleeding), type/number of individual wound complications, length of stay in hospital, and number of wound related hospital readmissions in the 30 days after surgery. Definitions and measures used for primary and secondary outcomes are included in supplementary table A.

Other secondary outcomes, including dressing related adverse events, such as rash, itchiness, and blistering, were assessed by research nurses. Serious adverse events (maternal death, admission to intensive care unit, life threatening condition) were monitored and reported to the human research ethics committee at each site. An independent Data Safety Monitoring Committee was established to assess the safety of the intervention. This committee, comprising an obstetrician, a statistician, and an infection control nurse specialist, oversaw the trial and reviewed interim analyses, undertaken twice during the life of the trial. The trial would not be stopped unless the committee deemed that significant safety problems were present during safety monitoring of the trial intervention.

Statistical analysis

We calculated the sample size on the basis of the proportion of women who developed an SSI within 30 days of caesarean section. On the basis of previous work in this area,[19] we conservatively estimated that 15% of women in the control group were likely to develop an SSI. Following discussions with infectious disease experts and obstetricians, we determined that an absolute reduction in the rate of SSI of 5 percentage points would be clinically important. The sample size needed to detect a reduction in the cumulative incidence of SSI at 30 days from 15% to 10% was

950 per group (90% power and 5% significance level; Power Analysis & Sample Size system (PASS, V.12), NCSS). We inflated the sample size by 10% to allow for loss to follow-up (n=1045 per group; total sample size 2090 women).

We summarised baseline characteristics comprising binary data by using counts and proportions and continuous data as mean and standard deviation or median and interquartile range, depending on the distribution. We used Cohen's κ to calculate inter-rater consistency between outcome assessors.

The pre-specified primary outcome analysis was by intention to treat. For women lost to follow-up and withdrawn from the study post-randomisation who were missing the primary outcome, we conservatively (favoured standard treatment, as it had higher levels of missing data) assumed that they did not develop an SSI (worst case analysis). As per the protocol, we explored differences in prognostic variables between groups. The prognostic factors assessed were identified in the literature[20 21] and based on expert opinion (body mass index, age, diabetes, smoking, rupture of membranes, parity, caesarean section elective/semi-urgent, and length of procedure). We found differences between groups relative to body mass index and group allocation. Thus, following the protocol, we analysed the primary outcome by using a logistic regression model, adjusting for these.

We used a planned per protocol analysis of treatment for device related and serious adverse events. We compared binary outcomes (that is, SSI, wound complications, adverse/serious adverse events) by using a χ^2 test or Fisher's exact test and risk ratios with 95% confidence intervals. We reported continuous variables with non-normal distribution (that is, length of surgery, length of stay in hospital) by using medians and interquartile ranges and compared them by using a Mann-Whitney U test. For all inferential tests, we considered a P value below 0.05 to be statistically significant.

Post hoc analyses

To check for the robustness of conclusions to the effect of assumptions around missing primary outcome data, we repeated the intention to treat analysis as described above assuming that all women missing the primary outcome did have an SSI (favouring closed incision NPWT; that is, best case analysis) and excluding women missing the primary outcome (complete case analysis). Additionally, we did a per protocol analysis excluding women lost to follow-up, women withdrawn after randomisation, and women treated against their randomised allocation (for example, treated with closed incision NPWT when in the standard dressing arm).

Secondary outcomes (type of SSI, wound complications, length of stay in hospital, readmissions, pain, reoperations) were analysed by complete case analysis (excluding women without primary outcome) and by per protocol analysis (as with the primary outcome: excluding women lost to follow-up, women withdrawn post-randomisation, and women treated against their randomised allocation).

Patient and public involvement

Patients were not involved in defining the research question or outcome measures or in the interpretation or writing up of results of this study. This study was conceived in 2013, when the patients as co-researchers movement had not widely been adopted in Australia.

Results

Between 26 October 2015 and 1 November 2019, 8558 of the 12 077 women screened were excluded, leaving 3519 women who were eligible. However, 338 (9.6%) could not be recruited as their caesarean section occurred after hours, and 1072 women were not enrolled for various reasons, including refusals, vaginal delivery, or delivery at another facility; 2109 (60%) women were enrolled. We randomly assigned 2035 women to receive NPWT (n=1017) or standard surgical wound dressings (n=1018) (fig 1). Follow-up concluded on 1 December 2019. Intention to treat analysis of primary and secondary outcomes (SSI, type of SSI, wound complications, length of stay in hospital, readmissions, pain, reoperations) included the 2035 women randomly assigned to the intervention and control groups.

Baseline demographic and obstetric characteristics were similar between groups (table 1). The average age of participants was 31 (SD 5.5; range 16-54) years. Half of all women (1012; 50%) had a pre-pregnancy body mass index of 35 or higher (range 30-72), and most (1472; 72%) had an elective caesarean section. One third of women (657; 32%) across the sample had either gestational diabetes or diabetes mellitus. At the time of caesarean section, most women (1729; 85%) had intact membranes. Most women (1942; 95%) had subcutaneous layer closure in addition to subcuticular (skin) closure; staples were rarely used (27; 1%). Inter-rater reliability between outcome assessors for the primary outcome SSI and the secondary outcome type of SSI yielded κ=0.764 (95% confidence interval 0.72 to 0.81), and κ=0.712 (0.66 to 0.76), respectively.

In the primary analysis, our "worst case" intention to treat analysis assumed that women whose primary outcome was missing did not develop SSI (table 2). The SSI rate across the entire sample was 8.6% (n=174). We observed a 3 percentage point reduction in the absolute risk of SSI in women treated with NPWT compared with standard dressings; this difference was not statistically significant (7.4% *v* 9.7%; risk ratio 0.76, 95% confidence interval 0.57 to 1.01; P=0.06) (table 2). In terms of SSI type, only 1 (<1%) woman in the NPWT group developed an organ/space SSI (table 2). The rates of all types of wound complications in the intervention and control groups were comparable. Wound dehiscence was the most common complication in both groups (10.6% *v* 10.1%; risk ratio 1.05, 0.81 to 1.36; P=0.71). More hospital readmissions occurred in the intervention group than in the control group, although this difference was not

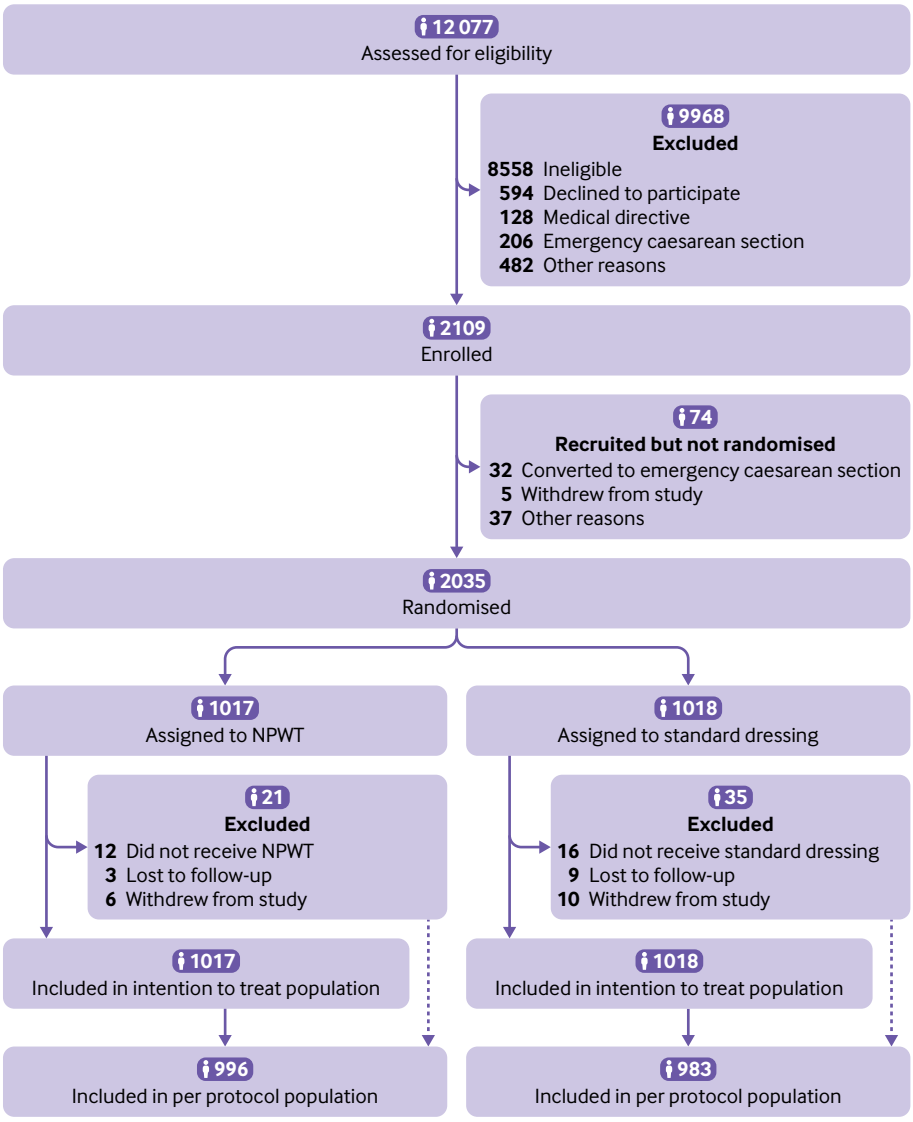

Fig 1 | Trial profile. NPWT=negative pressure wound therapy

statistically significant (2.3% *v* 1.3%; risk ratio 1.76, 0.90 to 3.46; P=0.09) (table 2).

No differences between the groups in the distribution of prognostic factors were apparent (table 1). Multivariable logistic regression analysis, including all a priori identified prognostic factors, showed that body mass index 40-49.9 (P=0.02) was a statistically significant model covariate (model likelihood χ^2=26.16, df 11; P<0.05; Nagelkerke R^2=2.9). The full results are shown in supplementary table B.

We did a planned per protocol analysis for dressing related adverse events and serious adverse events (table 3). Dressing related adverse events reported included skin blistering, itchiness, and rash. We observed a 2 percentage point increase in the absolute risk of skin blistering among women in the closed incision NPWT group, which was statistically significant (4.0% (40) *v* 2.3% (23); risk reduction 1.72, 1.04 to 2.85; P=0.03). Overall, 17 serious adverse events occurred, including three neonatal deaths. Rates of serious adverse events were low and did not differ between intervention and control groups (intensive care unit admission, life threatening condition: 1.2% *v* 0.5%; risk ratio 2.57, 0.92 to 7.17; P=0.06). Most of the admissions to intensive care related to the lack of available high dependency unit beds. One woman developed a pulmonary embolism. All serious adverse events were reported to the ethics board, and none was deemed related to the intervention.

Post hoc sensitivity analyses

Post hoc sensitivity analyses of the cumulative incidence of all types of SSI favoured closed incision NPWT therapy compared with our main crude analysis (reported above). The "best case" intention to treat analysis assumed that women with missing outcome data developed SSI (supplementary table C). The SSI incidence across the entire sample was 9.9% (n=202). We observed a 4 percentage point reduction in the absolute risk of SSI in women treated with closed

Table 1 | Baseline demographics and obstetric characteristics of intention to treat population (n=2035)

Demographic and obstetric characteristics	No (%) participants*		Risk difference (95% CI)
	Closed incision NPWT (n=1017)	Standard dressing (n=1018)	
Mean (SD) age†, years	31 (5.5)	31 (5.4)	0 (−0.47 to 0.47)
Pre-pregnancy body mass index‡:			
30.0-34.9	488 (48.0)	524 (51.5)	−3.49 (−9.61 to 2.64)
35.0-39.9	268 (26.4)	247 (24.3)	2.09 (−2.28 to 6.46)
40.0-49.9	218 (21.4)	211 (20.7)	0.71 (−3.28 to 4.70)
Smoker	101 (9.9)	117 (11.5)	−1.56 (−4.41 to 1.28)
Comorbidities:			
Gestational diabetes	292 (28.7)	288 (28.3)	0.42 (−4.21 to 5.06)
Diabetes mellitus	38 (3.7)	39 (3.8)	−0.09 (−1.78 to 1.60)
Hypertension	140 (13.8)	129 (12.7)	1.09 (−2.07 to 4.25)
Respiratory disease	124 (12.2)	142 (13.9)	−1.76 (−4.90 to 1.39)
Anaemia (Hb<110 g/L) in third trimester	99 (9.7)	83 (8.2)	1.58 (−1.02 to 4.18)
Diagnosed and treated depression	97 (9.5)	103 (10.1)	−0.58 (−3.30 to 2.14)
Thromboembolic disease	82 (8.1)	83 (8.2)	−0.09 (−2.56 to 2.38)
Hypercholesterolaemia pre-pregnancy†	10 (1.0)	4 (0.4)	0.59 (−0.13 to 1.31)
Immunocompromise (on immunosuppressive therapy)	4 (0.4)	5 (0.5)	−0.09 (−0.68 to 0.48)
Parity:			
0	233 (22.9)	264 (25.9)	−3.02 (−7.32 to 1.27)
1	358 (35.2)	374 (36.7)	−1.54 (−6.75 to 3.67)
2	247 (24.3)	202 (19.8)	4.44 (0.36 to 8.53)
≥3	179 (17.6)	178 (17.5)	0.12 (−3.52 to 3.76)
No of previous caesarean sections:			
None	381 (37.5)	421 (41.4)	−3.89 (−9.35 to 1.56)
1	379 (37.3)	383 (37.6)	−0.35 (−5.67 to 4.96)
2	186 (18.3)	156 (15.3)	2.97 (−0.60 to 6.53)
3	57 (5.6)	44 (4.3)	1.28 (−0.65 to 3.22)
≥4	14 (1.4)	14 (1.4)	0 (−1.02 to 1.02)
Status of membrane†:			
Intact	874 (85.9)	855 (84.0)	1.95 (−6.06 to 9.96)
Ruptured (≤12 h)	77 (7.6)	80 (7.9)	−0.29 (−2.70 to 2.13)
Ruptured (>12 h)	65 (6.4)	83 (8.2)	−1.76 (−4.11 to 0.58)
Surgery types:			
Elective caesarean section	740 (72.8)	732 (71.9)	0.86 (−6.53 to 8.25)
Semi-urgent caesarean section	277 (27.2)	286 (28.1)	−0.86 (−5.43 to 3.71)
ASA status:			
1	65 (6.4)	76 (7.5)	−1.07 (−3.36 to 1.21)
2	664 (65.3)	641 (63.0)	2.32 (−4.64 to 9.28)
3	283 (27.8)	294 (28.9)	−1.05 (−5.68 to 3.57)
≥4	5 (0.5)	7 (0.7)	−0.20 (0.86 to 0.47)
Median (IQR) length of surgery, min†	63 (51.0-77.0)	60 (49.0-75.0)	1.37 (−0.95 to 3.69)
Hair removal methods†:			
None	138 (13.6)	120 (11.8)	1.78 (−1.31 to 4.88)
Shaved	164 (16.1)	159 (15.6)	0.51 (−2.95 to 3.97)
Waxed	56 (5.5)	54 (5.3)	0.20 (−1.81 to 2.22)
Depilatory cream	5 (0.5)	2 (0.2)	0.30 (−0.21 to 0.80)
Clipped	653 (64.2)	682 (67.0)	−2.79 (−9.82 to 4.25)
Skin preparation†:			
Aqueous chlorhexidine	74 (7.3)	71 (7.0)	0.30 (−2.02 to 2.62)
Aqueous betadine	451 (44.3)	462 (45.4)	−1.04 (−6.86 to 4.78)
Alcoholic chlorhexidine	468 (46.0)	459 (45.1)	0.936 (−4.94 to 6.79)
Alcoholic betadine	22 (2.2)	25 (2.5)	−0.29 (−1.61 to 1.03)
Prophylactic antibiotics:			
Not given	8 (0.8)	12 (1.2)	−0.39 (−1.25 to 0.47)
Pre-incision	985 (96.9)	975 (95.8)	1.08 (−7.45 to 9.61)
Post-incision	24 (2.4)	31 (3.0)	−0.69 (−2.11 to 0.74)
Wound closure:			
Subcutaneous (fat) closure	966 (95.0)	976 (95.9)	−0.89 (−9.38 to 7.60)
Subcuticular (skin) suture	998 (98.1)	992 (97.4)	0.69 (−7.91 to 9.28)
Interrupted suture	7 (0.7)	9 (0.9)	0.20 (−0.97 to 0.57)
Staples (skin)	10 (1.0)	17 (1.7)	0.69 (−1.69 to 0.31)
Wound glue	2 (0.2)	0 (0)	−0.20 (−0.08 to 0.47)

ASA=American Society of Anesthesiologists; Hb=haemoglobin; IQR=interquartile range; NPWT=negative pressure wound therapy.
*Percentages might not add up because of rounding.
†Missing data for ≤5 women.
‡Weight in kilograms divided by square of height in meters.

Table 2 | Clinical outcomes for intention to treat population with missing data on primary outcome (28 women) assumed to be no surgical site infection (SSI), conservatively favouring standard care*. Values are numbers (percentages) unless stated otherwise

Clinical outcomes	All (n=2035)	Closed incision NPWT (n=1017)	Standard dressing (n=1018)	Relative risk (95% CI)	P value†
All SSI types	174 (8.6)	75 (7.4)	99 (9.7)	0.76 (0.57 to 1.01)	0.06
Superficial	163/174 (94)	70/75 (93)	93/99 (94)	0.75 (0.56 to 1.02)	0.72
Deep incision	10/174 (5.7)	4/75 (5)	6/99 (6)	0.67 (0.19 to 2.36)	0.72
Organ/space	1/174 (0.6)	1/75 (1)	0/99 (0)	-	0.50
Complications	247 (12.1)	123 (12.1)	124 (12.2)	0.99 (0.79 to 1.25)	0.95
Bleeding	30 (1.5)	14 (1.4)	16 (1.6)	0.88 (0.43 to 1.79)	0.72
Dehiscence	211 (10.4)	108 (10.6)	103 (10.1)	1.05 (0.81 to 1.36)	0.71
Haematoma	17 (0.8)	11 (1.1)	6 (0.6)	1.84 (0.68 to 4.94)	0.22
Seroma	53 (2.6)	27 (2.7)	26 (2.6)	1.04 (0.61 to 1.77)	0.89
Median (IQR) HLOS, days (n=2019)‡	3.0 (2.0-4.0)	3 (2.0-4.0)	3 (2.0-4.0)	-	0.32
Readmissions‡	36 (1.8)	23 (2.3)	13 (1.3)	1.76 (0.90 to 3.46)	0.09
Pain‡§	32 (1.6)	21 (2.1)	11 (1.1)	1.90 (0.92 to 3.93)	0.07
Reoperations‡¶	9 (0.4)	4 (0.4)	5 (0.5)	0.80 (0.22 to 2.96)	0.75

HLOS=hospital length of stay; IQR=interquartile range; NPWT=negative pressure wound therapy.
*Worst case analysis based on effect estimate; 28 women missing primary outcome data (12 lost to follow-up; 16 withdrawn) assumed not to have SSI (favouring standard dressing as this arm has higher levels of missing data).
†Using x^2 test, Fisher's exact test, or Mann-Whitney U test.
‡Data not available for randomised patients withdrawn from study.
§Pain associated with surgical wound requiring readmission measured as binary variable (yes/no).
¶5 participants had reoperations for wound complications before hospital discharge.

incision NPWT compared with standard dressings; this difference was statistically significant (8.3% (84) *v* 11.6% 118); risk ratio 0.71, 0.55 to 0.93; P=0.01). Results of the complete case analysis showed that the incidence of SSI across the whole sample was 8.7% (n=174). We observed a 3 percentage point reduction in the absolute risk of SSI in women treated with closed incision NPWT compared with standard dressings; this difference just reached statistical significance (7.4% (75) *v* 9.9% (99); risk ratio 0.75, 0.56 to 1.00: P=0.05) (supplementary table D). The results of the per protocol analysis that excluded women who did not have SSI outcome data were similar to the results of the complete case analysis (supplementary table E).

We also did a per protocol analysis of primary and secondary outcomes based on 1979 women (supplementary table E). In this analysis, we excluded the 56 women; 29 (1.4%) did not receive the allocated treatment, 16 (<1%) withdrew consent after randomisation (this included one woman who did not receive the allocated treatment), and 12 (<1%) women were lost to follow-up. The exclusion of 56 (2.7%) women (with missing data) in the per protocol analysis yielded results consistent with the intention to treat analysis for the SSI incidence (7.4% (74) *v* 10% (98); risk reduction 0.75, 0.56 to 1.0; P=0.05).

Discussion

On balance, the results of the four analytic scenarios suggest that closed incision NPWT may be effective in reducing SSI in obese women undergoing caesarean section. Our pre-specified primary analysis indicated that 9% of women in this trial developed an SSI of any type—7% in the closed incision NPWT group and 10% in the control group. This difference was close to statistical significance. The results of the best case, complete case, per protocol sensitivity, and multivariable analyses were consistent, favouring the closed incision NPWT intervention. The primary analysis was based on a conservative assumption that women lost to follow-up did not develop an SSI; this result showed a significant relative reduction of 29% in the cumulative incidence of SSI in the closed incision NPWT group. It is therefore possible that our primary

Table 3 | Safety and adverse events in per protocol population*. Values are numbers (percentages) unless stated otherwise

Clinical outcomes	All (n=1979)	Closed incision NPWT (n=996)	Standard dressing (n=983)	Relative risk (95% CI)	P value†
Dressing related adverse events					
Blistering	63 (3.2)	40 (4.0)	23 (2.3)	1.72 (1.04 to 2.85)	0.03
SSI and blistering	21/174 (12)	12/75 (16)	9/99 (9)	1.77 (0.79 to 3.97)	0.16
Itchiness and/or rash	13 (0.7)	10 (1.0)	3 (0.3)	3.29 (0.91 to 11.91)	0.09
Serious adverse events					
All	17 (0.9)	12 (1.2)	5 (0.5)	2.57 (0.92 to 7.17)	0.06
Neonatal deaths	3 (0.2)	2 (0.2)	1 (0.1)	1.97 (0.18 to 21.73)	1.00
ICU admissions	13 (0.7)	9 (0.9)	4 (0.4)	2.22 (0.69 to 7.19)	0.17
Life threatening condition	1 (0.1)	1 (0.1)	0 (0)	-	-

ICU=intensive care unit; NPWT=negative pressure wound therapy; SSI=surgical site infection.
*Per protocol population excludes participants (n=56) who were lost to follow-up (12 (<1%) participants), did not receive treatment to which they were originally allocated (28 (1%) participants), or subsequently withdrew from study (16 (<1%) participants). 1 participant withdrawn from study did not receive treatment to which she was originally allocated.
†Using x^2 test or Fisher's exact test.

analysis results underestimate the effectiveness of closed incision NPWT in this population, whereas, arguably, the results of the post hoc best case sensitivity analysis very likely overestimate its effectiveness. However, when the results of all analyses are considered together, closed incision NPWT seems likely to be effective in reducing SSI.

Comparison with other studies

Our results across all analytic scenarios were consistent, showing no significant differences in the incidence of superficial and deep SSI by trial arm. The results of other studies using closed incision NPWT in this population have yielded mixed results.[22-24] Variations in SSI rates as reported in other studies in this population are likely related to the different definitions used to classify and detect SSI,[20] smaller samples,[16 25] and use of pilot and cohort designs,[16 22 26] which carry a high risk of bias and uncertainty in the results. The results of several smaller trials in this population, some of which were non-blinded and industry funded, showed significant reductions of up to 50% in superficial SSI rates.[23 26 27] A recently updated Cochrane review of use of closed incision NPWT in primary wounds included a subgroup analysis of seven studies involving 1886 obese women undergoing caesarean section.[8] The results of that subgroup analysis indicated a 27% reduction, albeit non-significant, in superficial SSI incidence. The results of our trial, the largest in this field, suggest that closed incision NPWT may reduce superficial SSI incidence in this patient population. Given that approximately 29.7 million births occur through caesarean section globally,[2] this result is clinically important. However, the decision to use closed incision NPWT in this population needs to be considered alongside any economic benefit.

We found no statistically significant differences in organ/space SSI. Notably, this study was not powered to detect potential differences. Our results are similar to previous research in this population.[23 26 28] We also found no significant group differences in wound complications in relation to bleeding, dehiscence, haematoma, or seroma.

Implications of findings

The finding of a 72% relative increase in blistering associated with closed incision NPWT may have implications for healthcare decision making. The recently updated Cochrane review highlighted very low certainty evidence around blistering when comparing closed incision NPWT and standard dressings.[8] Whether blistering (under the adhesive dressing and tape) occurred because of the dressing itself or the adhesive tape that was applied (per manufacturer's instructions) around the dressing to reinforce the dressing and help to maintain suction is not clear. Results of several previous trials in this population reported adverse skin reactions including blistering, erythema, and bruising.[16 22 28] The occurrence of a minor treatable adverse event such as blistering that we found in this trial needs to be balanced with probable reductions in the incidence SSI. Thus, informing women about the potential risks of closed incision NPWT, and providing targeted training to clinicians in its application, may reduce the potential for blistering. Importantly, patients should be partners in the decision to use closed incision NPWT as an alternative wound management therapy.

The generalisability of our results needs to be considered relative to the inclusion criteria applied and the low rates of SSI in our study. We excluded women undergoing emergency caesarean section because they are a different population and their risk factors for SSI are not similar to those women undergoing elective and semi-urgent caesarean section.[21] Also, emergency caesarean section as a surgical procedure is much less "standardised" than other more "routine" caesarean procedures. Given the greater heterogeneity of women undergoing emergency caesarean section and of emergency caesarean section procedures, and wanting to increase internal validity to more precisely detect the potential impact of closed incision NPWT, we had to control for potential confounding variables as much as possible. Therefore, excluding these women meant that the caesarean procedure was more consistent in its technique and associated processes such as skin preparation and antibiotic use. In terms of SSI event rates, the baseline infection rate we found was much lower than we had assumed in our sample size calculation. Our trial was underpowered given the low event rate and thus may not be generalisable to other clinical settings. The women in this trial probably received a high standard of clinical care, based on clinical practice guidelines. However, the "true" rate of SSI is often underestimated using routinely collected surveillance data.[29] With the body of evidence for the effectiveness of closed incision NPWT growing, our findings may be useful for physicians' and women's decision making regarding dressing type irrespective of the centre's SSI rates.

Strengths and limitations of study

Strengths of this study include its sample size, the rigorous randomisation, and prospective data collection, including weekly follow-up by dedicated research staff. The results of a per protocol analysis were consistent with the intention to treat analysis, indicating minimal effect of missing data and loss to follow-up and the robustness of our results. Across both intervention and control groups, the time that dressings were left in situ was consistent, with both being intact for five days. Furthermore, SSI and wound complication outcomes were based on the definitions in the CDC's guideline.[18] The pragmatic nature of this trial and the characteristics of the dressings precluded blinding of participants, clinical staff, or data collectors. However, outcome assessors were blinded to group allocation and the intervention/comparator. The process of outcome ascertainment was rigorous: two blinded outcome assessors independently ascertained SSI and wound complication data, and a third outcome assessor adjudicated any discrepancies. Additionally, agreement

among outcome assessors was moderate. A Data Safety Monitoring Board provided oversight in terms of safety checks. This trial is also one of the few in this area that was not funded by industry, thus reducing potential biases relative to its conduct and reporting.

However, we note several limitations. Firstly, women undergoing urgent (category 1) caesarean section were excluded, despite this population having an even higher risk of developing a SSI.[21] We excluded these women because of ethical concerns related to trying to obtain valid consent. In most instances, these women would not have enough time to consider participation in this trial. Secondly, 60% of eligible women were enrolled and, of these, 73% had an elective caesarean section, affecting generalisability. Generalisability was maximised by recruiting women from four large public hospitals, who underwent both elective and semi-urgent caesarean section. The proportions of women undergoing elective versus semi-urgent caesarean section in Queensland public hospitals typically reflects the proportions recruited in this trial. Thirdly, over the four week data collection period, we were able to collect 30 day follow-up outcome data for all women except for the 16 women who withdrew their consent after randomisation. Fourthly, the potential exists for false positive or false negative outcome assessments of SSI and wound complications; however, blinding and use of two outcome assessors adjudicated by a third minimised this risk.

Fifthly, we followed up the women with telephone interviews. The decision to use telephone interviews was pragmatic; to bring women in weekly to assess SSI would have created an increased burden on participants and likely resulted in huge loss to follow-up. We used this approach in preference to having missing data. Also, we know that data from routine surveillance are inferior in quality to those from dedicated follow-up. The survey tool we used was a previously validated patient reported tool to assess for SSI.[30] It had a series of questions about signs and symptoms of SSI such as redness, pain/tenderness at the incision, and discharge, as well as questions related to involvement of health professionals in the management of the wound and antibiotics prescribed for the wound. To ensure the quality and consistency of the data, research nurses used an interview script based on SSI symptoms and related resource use. Additionally, to minimise loss to follow-up, the research nurses contacted women on three separate occasions for each week if the women did not answer. Other research has shown that self-report of wound related complications is accurate when validated tools are used.[17 30] We cannot rule out the possibility that trial participants may have incorrectly reported their wound characteristics, but we have no reason to think that this was likely to occur.

Sixthly, we did not do time analysis because reporting time to SSI using weekly data provides limited information. Seventhly, despite the large sample size, the cumulative incidence of SSI was lower than expected; thus, given the wider 95% confidence intervals (less precision) for the primary outcome, a false negative result (type II error) is still possible. Furthermore, underestimation of the incidence of SSI is possible, given the way that missing data have been treated in the analysis of primary analysis. Finally, we did not have access to general practice data or information as to whether women went back to different hospitals or on any use of antibiotics for wound infection. Therefore, some wound complications and infections may have been missed, leading to an underestimation of SSI incidence. Nevertheless, the women in this study were able to accurately self-report any wound related complications and treatments (for example, antibiotics).

Conclusions

On the basis of our primary intention to treat analysis, assigning no SSI to missing data, prophylactic closed incision NPWT for obese women after caesarean section resulted in a 24% reduction in the relative risk of SSI compared with standard dressings (3% reduction in absolute risk). This difference, although close to statistical significance, possibly underestimates the effectiveness of closed incision NPWT in this population. On balance, the results of the conservative primary, multivariable adjusted model, and post hoc sensitivity analyses should be considered alongside the growing body of evidence of the benefits of closed incision NPWT and given the number of obese women undergoing caesarean section globally. However, the decision to use closed incision NPWT needs to be weighed against the increase in skin blistering and economic considerations and based on shared decision making.

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Data sharing: Access to individual patient level data is not available for this study. The published protocol can be found at https://bmjopen.bmj.com/content/6/2/e010287.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results have been and will be presented at national and international conferences. Dissemination plans to inform the patient community of this study's results include social media, press release, and the hospital's newsletter. Study results will be disseminated to the trial participants by email or letter upon their request.

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Web appendix: Supplementary tables