Abstract

Aims

This study sought to provide estimates for the different rates of deep surgical site infection as measured by the Centres for Disease Control definition after hip fracture surgery between patients treated with either incisional Negative Pressure Wound Therapy (NPWT) or standard wound dressings. Secondary objectives included determining recruitment rate and willingness to participate in the trial.

Patients and Methods

A two group multicentre randomised controlled feasibility trial embedded in the World Hip Trauma Evaluation cohort study. Any patient over the age of 65 years having surgery for hip fracture was considered at 5 recruitment centres in the United Kingdom. Patients were randomly allocated to either incisional NPWT or standard dressings after closure of the surgical wound.

The primary outcome measure was deep Surgical Site Infection at 30 and 90 days diagnosed according to the criteria of the Centers for Disease Control and Prevention. Secondary outcomes were: rate of recruitment, further surgery within 120 days, health-related quality of life (HRQOL) measured using the EQ5D-5L tool and related complications within 120 days as well as mobility and residential status at 120 days.

Results

462 valid randomisations were carried out (232 and 230 respectively in the incisional NPWT and standard dressing groups). In the standard dressing group, 14 patients developed deep SSI out of 218 analysed (6.4%). In the incisional NPWT group 4 patients developed deep SSI out of 214 analysed

(1.9%). This gives a total SSI event rate of 4.2% (95% CI 2.7%-6.5%). Patients and surgeons were willing to participate in this study with 462 patients recruited from a possible 749 cases (62.3%).

Conclusions

The estimated rate of deep surgical site infection 30 days after hip fracture surgery was 4%, which makes a study comparing the clinical effectiveness of incisional NPWT to standard dressings feasible.

Ethics and dissemination Oxford C Research Ethics Committee granted ethical approval on 28/04/2017, 17/ SC/0207. ISRCTN55305726.

Background

Hip fracture is one of the biggest challenges facing elderly patients and healthcare systems. Worldwide there are 1.3 million hip fractures and more than 60,000 occur in the UK every year (1). ~~These figures are projected to rise to >100,000 by 2020 in the UK (1).~~

The cornerstone of the acute patient care in high income settings is the surgical management of the hip fracture (2). Surgery seeks to restore patients mobility as quickly as possible and is used in over 98% of hip fracture cases in the UK and other high income settings (2).

Given the high prevalence of comorbidity and frailty(3, 4), it is unsurprising that complications are common in hip fracture care(5). One of the most devastating complications is deep surgical site infection (SSI), which is associated with 20% increased mortality at one year as well as longer length of stay and higher inpatient care costs(6). The consequences have been realised by stakeholders in hip fracture care and prevention of deep SSI is now a major research priority(7).

Wound management is an important component of reducing SSI. There is a growing body of literature that suggests incisional Negative Pressure Wound Therapy (NPWT) may reduce the risk of SSI(8, 9).

Given the devastating consequences of SSI in hip fracture, and the possibility of benefit with incisional NPWT, a fully powered randomised controlled trial assessing effectiveness is a high priority. The limitations around the true rate of SSI, which have been reported as being between 1% and 9% preclude an informed sample size calculation(10, 11).

Our aim was to estimate the different rates of deep surgical site infection (SSI) after hip fracture surgery between patients treated with incisional NPWT and standard dressings.

Methods

TRIAL SUMMARY

This study was embedded within the World Hip Trauma Evaluation (WHiTE) cohort study(12-19). The National Research Ethics Service approved the study (28/04/2017, 17/ SC/0207); Full study details are in the published protocol(20). The trial was overseen by independent steering and data and safety monitoring committees.

CONSENT

Patients with a hip fracture are a clinical priority for urgent operative care. They undergo surgery on the next available trauma operating list. All patients with a hip fracture are in pain and have received opiate analgesia. It is therefore understandable that the majority of patients find the initial period of their treatment in hospital confusing and disorientating. Similarly, patients' next of kin, carers and friends are often anxious at this time and may have difficulty in weighing the large amounts of information that they are given about the injury and plan for treatment. It is often not possible for the patient or relative/carer (consultee) to review trial documentation, weigh the information and communicate an informed decision about whether they would wish to participate. The consent procedure for this trial reflected that of the surgery, with the clinical team assessing capacity before taking consent for

the surgical procedure and this capacity assessment then being used to inform consent for the research study. An appropriate method, in line with the Mental Capacity Act, was then used to gain either prospective or retrospective consent from the participant or appropriate consultee by a GCP-trained, appropriately delegated member of the local research team.

INCLUSION AND EXCLUSION CRITERIA

Eligible patients were aged 65 years or older and having surgery to fix a hip fracture. Patients were excluded if they had cannulated screw fixation of an undisplaced intracapsular fracture of the hip due to the small incisions needed for this procedure.

RANDOMISATION

A computer-generated randomisation algorithm was created and delivered by an accredited Clinical Trials Unit to ensure that the allocation sequence was concealed. The individual patient was allocated to treatment on a 1:1 basis, stratified by recruitment centre.

Participants were assigned their allocated treatment intraoperatively at the end of surgery, but before any wound dressings were applied.

Participants were not blinded to their treatment allocation as wound dressings were clearly visible. In addition, the treating surgeons could not be blind to the intervention, but the surgical and healthcare team were not involved in any trial assessments and the primary outcome data were collected by independent research associates.

Interventions

All patients received a general or regional anesthetic. The operative treatment followed standard clinical practice with relevant details recorded by the research team. Routine prophylactic antibiotics according to local hospital policy were given to all patients. This was either a single intraoperative dose (two centres) or multiple doses (two centres). All patients were assessed for venous thromboembolism prophylaxis according to local policy. At the end of the operation, the allocated dressing was applied to the surgical wound. All other elements of postoperative care and rehabilitation were the same for all patients.

Standard Dressing Group. All recruitment centres used a sterile dressing sealed from external contamination. However, the precise details of the materials used were left to the discretion of the treating healthcare team as per routine care at their centre.

Incisional NPWT group. The PICO (Smith and Nephew Plc) dressing system was the device used in the Incisional NPWT arm. Incisional NPWT uses a silicone contact layer with a silicon-based adhesive, an airlock layer, a superabsorbent layer and a polyurethane (semipermeable) layer on the top which makes the system showerproof while allowing water vapour to pass. A sealed tube connects the dressing to a built-in mini-pump that creates a partial vacuum (-80 mmHg of negative pressure) over the wound. Incisional NPWT was applied to the wound at the end of the operation as per the treating surgeon's normal practice and according to the dressing manufacturer's instructions; any further wound dressing was recorded and followed the allocated treatment unless otherwise clinically indicated.

DATA COLLECTION AND OUTCOME MEASURES

Primary Outcome: The primary outcome measure for this study is deep surgical site infection; We used the CDC definition of a “deep surgical site infection”, that is a wound infection involving the tissues deep to the skin that occurs within 30 or 90 days of surgery (21). The participants were assessed by an independent research associate who recorded the primary outcome against the CDC criteria for the diagnosis of deep infection: 1. Fluid was leaking from the wound, and the fluid was pus. 2. At least one criterion from EACH of the following lists was satisfied: a. The wound was gaping open (dehisced) OR a surgeon had deliberately opened the wound; b. The area around the wound was painful or tender OR the participant had a fever >38°C; 3. There was any sign of abscess or infection on direct examination or imaging.

The addition of 90 day follow up is a recent change in the CDC criteria. Therefore to satisfy the appropriate criteria each patient was at assessed at both 30 days and 90 days (22).

Secondary Outcomes:

Recruitment The rate of recruitment of potential participants, both in terms of eligibility and those who consent (or on whose behalf consent was provided) was recorded and reported. Number of available patients and proportion recruited is an informative feasibility parameter.

Further Surgery Any further surgical interventions to the hip were recorded from the patient and medical record if they were within 120 days of the index hip fracture.

Complications were collected if on the following pre-defined list: wound infection, respiratory infection, urinary tract infection, venous

thromboembolism, cerebrovascular accident, cardiac event, failure of fixation, dislocation, blood transfusion and were collected from the medical record and included only if they were within 120 days post randomisation

The core outcome set for hip fractures was also captured(23):

Mortality Death within 120 days was recorded from the medical record.

Health Related Quality of Life. This was measured using the EuroQol EQ-5D-5L tool at baseline and 120 days. The EQ-5D-5L is a validated self-administered patient-reported outcome measure. EQ-5D is a generic health-related QoL measure consisting of five dimensions each with a five-level answer possibility. Each combination of answers produces a health profile which can be converted into an estimated health utility score after applying a set of preference weights. A scoring which maps the EQ-5D-5L to EQ-5D-3L value sets was used and the EUROQOL calculator was used(24, 25). This score was completed either by the patient or a carer if they lacked capacity.

Mobility Pre-fracture and current mobility status was collected at 120 days. The possible responses for mobility status were: freely mobile without aids, mobile outdoors with one aid, mobile outdoors with two aids or frame, some indoor mobility but never goes outside without help, no functional mobility (using lower limbs).

Residential status Pre-fracture and current residential status will be collected at 120 days. The possible responses for residential status are: own home/sheltered housing, residential care, nursing home, rehabilitation unit, acute hospital, dead, other.

STATISTICAL ANALYSIS

Standard statistical summaries (e.g. means, standard deviations, medians, IQR) are reported for all discrete and continuous outcome measures. Baseline data (e.g. age and gender) were summarized to check comparability between treatment groups. No formal hypothesis testing took place; as per the aim of this feasibility study, the analysis reports the deep SSI rates overall and in the two treatment groups on an intention-to-treat basis at 30 days and 90 days post-recruitment. Analysis of between group rates of deep SSI was exploratory in this feasibility study. Any between group differences are *'post hoc'* and were interpreted in this context. These differences were presented using descriptive statistics, and appropriate measures of uncertainty (e.g. 95% confidence intervals). All analyses were undertaken using STATA 15.1 (Stata Corp, College Station, TX)(26). Binomial confidence intervals were calculated using the Wilson method (27).

Feasibility was shown if the rate of deep SSI in the feasibility data was sufficiently high that a clinically important difference could be shown, and that the number of patients needed to do this would be realistic.

Results

Primary outcome-Intention to Treat

There was a total rate of 18 deep SSIs in 432 patients, giving an overall rate of 4.2% at 30 days (95% CI 2.7%-6.5%). The rate of deep SSI at 30 days was 6.4% (14/218) in the standard dressing group and 1.9% (4/214) in the incisional NPWT group (Risk ratio 0.29; 95% CI 0.10 to 0.85).

At 90 days the rate of deep SSI was 6.4% (14/218-) in the standard dressing group and 2.3% (5/214) in the incisional NPWT group, 4.4% overall (95% CI 2.8%-6.8%).

When considered on a ‘per protocol’ basis, the rates of 30 day deep SSI were as follows: Total rate of 15 infections in 307 patients, giving an overall rate of 4.6% at 30 days (95% CI 2.8%-7.5%). The rate of deep SSI at 30 days was 6.5% (11/168) in the standard dressing group and 2.6% (4/156) in the incisional NPWT group (Risk ratio 0.39 ; 95% CI 0.13 to 1.20). The ‘per protocol’ rate of deep SSI at 90 days was 17 infections in 324 patients a rate of 5.2% (95% CI 3.3%-8.2%). By group it was 7.7% (13/168) in the standard dressing group and 2.6% (4/156) in the incisional NPWT group. All deep SSI outcome data are reported by group in table 2.

Secondary outcomes

Recruitment and retention

Four hundred and sixty two patients were recruited successfully into the study between July 2017-February 2018. Five patients were randomised in error and withdrawn (467 randomisations in total). Figure 1 outlines the CONSORT diagram.

The patients recruited into this study were representative of the broader population of patients with hip fractures in terms of age, gender and anaesthetic risk (Table 1)(18). These characteristics were well balanced by the randomisation process. Similarly, the surgical treatment delivered was balanced between both study groups, and included a representative spread of arthroplasty and internal fixation treatments by a mix of training and consultant surgeons.

The process of recruitment is outlined in supplementary figure 1. Thirty-one patients withdrew, of which 30 withdrawing prior to the primary outcome data collection at 30 days.

Further surgery

The mainstay of further surgical intervention in these patients was debridement of the wound (7/305 (2.3%)). Three patients underwent revision surgery within the 120 day follow up period (3/313 (1.0%)).

Complications

There was a similar pattern of complications for the treatment groups. Most commonly patients suffered from infection of the chest or urinary tract or required blood transfusion. Further data on complications, mobility and residential status are reported in supplementary tables.

Core Outcome Set

Health Related Quality of Life: The mean EQ-VAS score was 67.7 (SD 22.3) in the incisional NPWT group (n=163) and 69.1 (SD 21.4) in the standard dressing group (n=171). The mean EQ-5D index was 0.46 (SD 0.37) in the incisional NPWT group (n=206) and 0.48 (SD 0.37) in the standard dressing group (n=209). All-cause mortality at 30 days was 33 patients out of a possible 432 (7.6%), there were 17 of 218 deaths (7.8%) in the incisional NPWT group and 16 of 214 (7.5%) in the standard dressing group

Discussion

The objectives for this study were to assess each patient against the CDC criteria for deep SSI in those allocated to either incisional NPWT or standard dressings in a randomised feasibility trial. Secondary objectives were to understand recruitment and retention, the nature of further surgery for cases of deep SSI. There were 18 cases of deep SSI in 432 patients at 30 days - a rate of 4.2%. Half of the participants with a deep SSI underwent further

surgery in the study window (n=9). Patients, site study teams and clinical teams were able to recruit 462 patients over a 6 month period.

The feasibility objectives have been met and a fully powered study comparing incisional NPWT to standard dressings can be deemed feasible on the basis of these data.

A deep SSI rate of 4.2% in hip fracture surgery is a critical benchmark metric for powering a full scale randomised study looking at incisional negative pressure wound therapy in hip fracture patients. If a reduction of 1.5% in the rate of SSI (to 2.7%) were sought, a total study population of 6,220 would be needed. This can be considered feasible on the basis of the recruitment rate achieved in this feasibility study and the number of centres available to the WHiTE cohort. Given the profound consequences of deep SSI in hip fracture patients, such a study would be of value to patients and healthcare systems.

The small numbers of patients in each group, lack of statistical power and feasibility design of this study preclude a clinical effectiveness recommendation on the basis of these data.

The only previous study of incisional NPWT in the hip fracture population compared the presence of seroma and dressing requirements(28). Here the observed effect was in favour of the incisional NPWT in reducing the size of the seroma.

This is in the context of meta analyses which seem to suggest a treatment benefit across multiple forms of surgery for incisional NPWT(8, 9). However, each population may benefit differently as they will likely have different risks. Other large scale studies of incisional NPWT in major orthopaedic trauma have failed to show a clinically important difference in deep SSI(29).

There were no significant issues with patient recruitment, retention and clinician engagement. The study centres had a high volume of eligible cases and as such any definitive study should be able to recruit a representative sample of patients in an appropriate timescale.

Further surgical procedures are a significant cost driver and source of patient co-morbidity. As such they remain an important parameter to consider in any definitive health economic analysis. That not all patients with deep SSI underwent further surgery in this study may reflect that some patients were deemed too high risk for surgical treatment. In addition this feasibility study only captured data up to 120 days in line with the embedded cohort framework (12). Any definitive study may benefit from a longer follow up period or augmented data collection in order to capture reoperation data for a more extensive period of time.

The core outcome set data were successfully captured, and no difference was noted in between treatment groups in terms of mortality and complications. The collection of data around health related quality of life will be crucial in informing the cost effectiveness calculations of incisional NPWT if clinical superiority were demonstrated in a definitive trial.

Strengths

Whilst the 462 patients sample size can be considered large for a feasibility study, it was still relatively small to capture a ‘rare’ outcome. This is reflected in the broad confidence intervals for both the treatment groups and the total study population. The main strengths of this study relate to the inclusion of a highly representative patient cohort. In particular the inclusion of patients with cognitive impairment, who make up 40% of the hip fracture population(30).

This group of patients is typically difficult to include in randomised studies due to legal and practical issues. The situation of this feasibility trial within the WHiTE cohort made it possible to overcome these barriers as there is significant expertise on this issue (12).

The baseline characteristics of the patients included in the study demonstrate that they are representative of both the broader WHiTE cohort as well as similar national data sets such as the National Hip Fracture Database(2, 30).

Limitations

The inclusion of patients with cognitive impairment may augment the withdrawal rate as patients are recruited under the agreement of a consultee. For an outcome such as deep SSI, accounting for each case is critical due to the low event rate relative to the study population. Methods such as multiple-imputation are limited in dealing with these types of data loss as they propagate observed data and do not take into account any variation between the withdrawn and retained study populations.

Conclusion

A definitive randomised clinical comparing incisional NPWT with standard dressings in hip fracture patients is deemed to be feasible on the basis of the deep SSI rate seen across treatment groups. There were no significant issues in recruitment, retention or data capture. Given the devastating consequences of deep SSI for hip fracture patients, such a study should be considered a priority.

334**Table 1 Baseline patient and treatment characteristics by treatment**

335**group.**

Characteristic	Standard Dressing (n=230)	iNPWT (n=232)	
Age (Median and IQR)	84.9(77-89)	85.2(77-90)	
Gender (F:M)	73%: 27%	69%: 31%	
ASA I	3 (1.4%)	5 (2.3%)	
ASA II	54 (24.5%)	52 (23.4%)	
ASA III	129 (58.6%)	125 (56.3%)	
ASA IV	33(15.0%)	40 (18%)	
ASA V	1 (0.5%)	0(0.0%)	
Mean preop AMTS (SD)	8.0 (3.0%)	7.4 (3.5%)	
Own home	185 (85.6%)	177 (82.3%)	
Residential care	16 (7.4%)	17 (7.9%)	
Nursing home	10 (4.6%)	19 (8.8%)	
Other	5 (2.4%)	2(1.0%)	
Regular Smoker			
Y	15 (7.0%)	21 (10.0%)	
N	198 (93.0%)	190 (90.0%)	
Diabetic			
Y	24 (12.6%)	34 (18.9%)	
N	190 (87.4%)	179 (81.1%)	
Surgery <36 Hours	129 (56.1%)	143 (61.6%)	272 (58.9%)
Operation			
Hemiarthroplasty (Cemented)	113 (49.3%)	118 (51.1%)	231 (50.2%)
Hemiarthroplasty (Uncemented)	2 (0.9%)	3 (1.3%)	5 (1.1%)
Arthroplasty - THR (Cemented)	11 (4.8%)	9 (3.9%)	20 (4.3%)
Arthroplasty - THR (Uncemented)	0 (0%)	1 (0.4%)	1 (0.2%)
Arthroplasty - THR Hybrid	15 (6.6%)	13 (5.6%)	28 (6.1%)
Internal Fixation - Cannulated Screws	2 (0.9%)	5 (2.2%)	7 (1.5%)
Internal Fixation - IM Nail	15 (6.6%)	17 (7.4%)	32 (7.0%)
Internal Fixation - Sliding Hip Screw[a]	71 (31.0%)	65 (28.1%)	136 (29.6%)
Surgeon Grade			
Consultant	153 (66.5%)	156 (67.5%)	309 (67.0%)
ST3 +[b]	66 (28.7%)	66 (28.6%)	132 (28.6%)
SAS	11 (4.8%)	9 (3.9%)	20 (4.3%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Wound Closure			
Interrupted	26 (15.5%)	16 (9.8%)	42

Suture			(12.7%)
Skin Clips	25 (14.9%)	26 (16.0%)	51 (15.4%)
Subcuticular Suture	111 (66.1%)	117 (71.8%)	228 (68.9%)
Other	6 (3.6%)	4 (2.5%)	10 (3.0%)

[a] *Within the sliding hip screw cohort were patients co enrolled in another embedded trial, which included a similar device. All patients were classified as receiving sliding hip screw(17)*

[b] ***ST3 denotes a training grade surgeon equivalent to resident***

Table 2 : Comparison of treatment groups on primary and secondary outcomes.

	Incisional Negative Pressure Wound Therapy		Standard dressing		
	Summary[a]	N	Summary[a]	N	
30 days as randomised population (available cases)	4 (1.9%)	214	14 (6.4%)	218	
30 days Per Protocol population (available cases)	4 (2.8%)	144	11 (6.7%)	163	
90 days as randomised population (available cases)	5 (2.3%)	214	14 (6.4%)	218	
Secondary outcomes					
Mortality					
30 days	16 (7.4%)	214	17 (7.8%)	218	-
120 days	36 (17.0%)	211	43 (19.9%)	216	-
EQ-VAS (as randomised population, available cases)[b]					
Baseline	68.6 (20.0)	202	71.3 (19.1)	205	-
120 days	67.7 (22.3)	163	69.1 (21.4)	171	-
EQ-5D index (as randomised population, available cases)[c]					
Baseline	0.69 (0.28)	201	0.73 (0.27)	206	
120 days	0.46 (0.37)	206	0.48 (0.37)	209	

[a]Summaries are n (%) for binary and mean (95% CI) for continuous variables.
[b]EQ-5D VAS range from 0 to 100 with higher scores indicating better quality of life.
[c]EQ-5D utility scores range from -0.594 to 1 with higher scores indicating better quality of life. Scores were converted to multi-attribute utility values using the crosswalk and EQ-5D-3L value sets.

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