**Chlorhexidine dressings could reduce external ventricular drain infections: results from a systematic review and meta-analysis**

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**Abstract**

**Background**. The incidence of external ventricular drain (EVD) infections remains high. Chlorhexidine dressings have demonstrated efficacy in reducing infections associated with indwelling catheters at other body sites, although evidence for their use with EVDs is limited.

**Aim**. The aim of this systematic review and meta-analysis was to evaluate the efficacy of chlorhexidine dressings in reducing EVD associated cerebrospinal fluid infection (EVDAI).

**Methods**. Systematic review and meta-analysis. MEDLINE, EMBASE and the Cochrane library were queried for articles from inception. The primary outcome was the incidence of EVDAI. Secondary outcomes included device safety, microbiological outcomes and shunt-dependency.

**Findings**. From 896 unique records, 5 studies were included of which 4 presented suitable data for quantitative analysis including three case series and one underpowered randomised controlled trial. There was a high risk of bias in most studies. 880 patients were included with a mean age of 57.7 years (95% CI 57.4-58.0 years). In primary outcome analysis, the chlorhexidine dressing group had a significantly lower incidence of EVDAI (1.7% vs. 7.9%, RD = 0.07, 95% CI 0.00 – 0.13, p = 0.04).

**Conclusion**. Chlorhexidine dressings may reduce the incidence of EVDAI but require future study in randomised trials to definitively determine efficacy.

**Short title**

Chlorhexidine dressings for EVDs

**Key words**

External ventricular drain; EVD; chlorhexidine; dressing; Biopatch

**Introduction**

An external ventricular drain (EVD) or ventriculostomy is the most commonly performed neurosurgical procedure worldwide.1 Although practice varies internationally, the commonest indications for an EVD include intracranial haemorrhage and traumatic brain injury.2 Patients with EVDs have a risk of developing infection which can lead to secondary brain injury, which is associated with a worse clinical outcome, longer hospital stay and increased health care costs.3, 4

Several studies have compared various treatment strategies to reduce the rate of EVDAI including prophylactic periprocedural antibiotics, silver and antibiotic impregnated catheters and prolonged post-procedural antibiotics.5-10 However, not all of these measures have demonstrated efficacy in reducing EVDAIs,5, 10 and contemporary data indicates that despite these measures the rate of EVDAI is still around 10%.2, 11

Most EVDAIs are caused by skin commensals such as coagulase negative Staphylococcus.2 These could be introduced intracranially either at the time of EVD insertion, or subsequently through ventricular catheter colonisation or improper drain care or sampling technique. Chlorhexidine is a broad-spectrum antiseptic that can be impregnated into dressings, which have reduced colonisation around indwelling catheters, such as arterial lines and central lines, and catheter related infections.12 There is also some evidence that chlorhexidine dressings could reduce EVDAIs.13 Chlorhexidine dressings that are commonly used include standard shaped dressings and disc-shaped foam impregnated dressings (Biopatch®). However, dressing choice is often not addressed in EVD care surveys and bundles designed to reduce EVDAIs, with few studies on the matter.14 We therefore undertook a systematic review and meta-analysis to evaluate the efficacy of chlorhexidine dressings in reducing EVDAIs.

**Methods**

**Registration**

The study protocol was registered on the international prospective register of systematic reviews (PROSPERO) under the ID number: CRD42021238626. The review was undertaken, and the manuscript prepared according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.

**Literature search**

The literature search strategy is outlined in the Supplement. All searches were conducted by two independent authors (MW and AC). MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews were queried from inception to 03/12/2020 using the NICEHealthcare Databases Advanced Search (HDAS) service. References of included studies were examined to extract potential further papers that may have been missed during the initial systematic search. Two independent authors (MW and AC) screened titles and abstracts independently and blindly to identify articles meeting the inclusion criteria. Discrepancies were resolved through discussion and review by a 3rd author (AII).

**Article inclusion: PICO**

Articles meeting the following criteria were included in the study, grouped as per our Participants, Interventions, Comparisons and Outcomes (PICO) strategy:

* Participants:
	+ Patients of all ages
	+ Undergoing an external ventricular drain for any reason
* Interventions
	+ Chlorhexidine dressing of any type including Biopatch®
* Comparison (in quantitative analysis)
	+ No chlorhexidine dressing
* Outcome
	+ EVDAI at any time point

**Data extraction**

Data relating to patient demographics, baseline characteristics, EVD protocol and that relating to the primary/secondary outcomes were extracted into an Excel spreadsheet.

**Outcomes**

The primary outcome was EVDAI provided as a function of number of patients. This was defined as a single positive CSF culture result +/- clinical suspicion of a CSF infection. This definition was applied uniformly to studies as some required confirmatory CSF culture. Secondary outcomes included safety considerations (for this analysis, studies had to explicitly report the presence or absence of adverse events e.g. contact dermatitis), ventricular catheter colonisation, microbiological profile of CSF infections and shunt dependency. Skin commensals were defined as common species of Staphylococcus (e.g. coagulase-negative Staphylococcus). Further information on outcome definitions is provided in Supplementary Table 1.

**Risk of bias**

For randomised controlled trials, the risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB 2).15 For non-randomised studies including a non-chlorhexidine group, the risk of bias was assessed using The Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I).16

**Statistical analysis**

Statistical analysis was performed using SPSS version 22 (IBM Corp., Armonk, NY). Means were weighted by study sample size due to the paucity of reported variance. Group comparisons were performed using independent t-tests (t-t). Meta-analysis for the primary outcome was performed using RevMan version 5.4 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.). The primary outcome analysis involved a dichotomous outcome meta-analysis using a Mantel-Haenszel method and random effects model due to the low incidence of EVDAIs. A risk difference model was used rather than odds ratio due to zero events in one of the included studies.17 Secondary outcome measures were summarised by providing the rate of each event.

**Results**

**Study characteristics**

896 unique records were identified from which 38 full texts were screened (Figure 1). Five studies described the rate of EVDAI with chlorhexidine dressings (Table 1).13, 18-21 Four studies included a control group so were included in meta-analysis: one randomised controlled trial evaluating generic chlorhexidine dressings and three case series evaluating Biopatch®. The remaining case series that evaluated generic chlorhexidine dressings was included in secondary outcome analysis.

**Risk of bias**

The included randomised controlled trial had a high overall bias with a high risk of bias in deviations from the intended interventions due to exclusion of participants, some risk of bias in the randomisation process and low risk of bias in other domains (Supplementary Figure 1). This study was also underpowered and post-hoc analysis revealed a study power of only 38%. All case series included in quantitative analysis had a high risk of bias as they included historical comparator groups subject to selection bias and introduced a change in practice in several variables that could relate to the primary outcome (Table 1).

**Primary outcome: EVDAI**

880 patients were included across four studies (Table 2). The mean age was 57.7 years (95% CI 57.4-58.0 years). 93% of patients in the chlorhexidine dressing group also had antibiotic impregnated catheters. The rate of infection was unknown in the control group. The mean EVD duration was 9.0 days (95% CI 8.9-9.1 days). The chlorhexidine dressing group had a longer EVD duration (9.6 days vs. 8.7 days, t-test, t = 7.66, p < 0.001). In primary outcome analysis (Figure 2), the chlorhexidine dressing group had a significantly lower incidence of EVDAI (7/411 [1.7%] vs. 37/469 [7.9%], risk difference = 0.07, 95% CI 0.00 – 0.13, p = 0.04). There was significant heterogeneity in the data (I2 = 68%).

**Secondary outcomes**

*Safety considerations*. The rate of adverse events with chlorhexidine dressings was 0/44 patients, as explicitly reported in only two studies.13, 20 One study measured CSF concentrations of chlorhexidine in 16 patients after 48 hours of a generic chlorhexidine dressing, finding CSF levels to be undetectable (<0.1ug/l) in all 16 samples evaluated.20

*Microbiological outcomes*. Colonisation of the ventricular catheter was evaluated in one study and found to be significantly lower in patients randomised to chlorhexidine dressings (5/21, [24%] vs. 9/20 [45%]).13 CSF culture results were reported in 3 studies.13, 19, 21 Skin commensals were cultured from the CSF from only one patient in the chlorhexidine dressing group versus 10 times from 9 patients in the non-chlorhexidine dressing group. Non skin commensals were cultured from the CSF from only one patient in the chlorhexidine dressing group (Streptococcus Pneumonia). These were more frequent in patients without a chlorhexidine dressing including Stenotrophomonas maltophilia (n = 1), Enterococcus (n = 2), Candida species (n = 1), Exophiala spinifera (n = 1) and Klebsiella (n = 1). Microbiological culture results were reported too infrequently to allow a meaningful statistical comparison.

*Shunt dependency*. Shunt dependency was described in two studies.13, 19 The overall risk of shunt dependency was not statistically different between the chlorhexidine dressing group (21/84, 25%) and non-chlorhexidine dressing group (51/245, 21%; Fisher’s Exact, p = 0.45).

**Discussion**

The data from this systematic review and meta-analysis shows that there is currently limited quality evidence evaluating the efficacy of chlorhexidine dressings in the context of EVDAI. It is possible that chlorhexidine dressings could reduce the risk of EVDAI, but the literature is not compelling.

Our primary outcome analysis revealed that the chlorhexidine dressing group had a significantly lower rate of EVDAI. However, chlorhexidine dressings were used alongside EVD care bundles in 3 out of the 4 studies included in this analysis, which included interventions that could have influenced the rate of EVDAI. The efficacy of bundles containing chlorhexidine dressings could suggest a synergy when these dressings are used alongside interventions such as silver and antibiotic impregnated catheters. There is evidence that such bundles of care can reduce perioperative infection risk in general.22 Elsewhere in the body, there is robust class 1 evidence to support the use of chlorhexidine dressings, such as for central venous catheters.23 In the central nervous system, experience is limited, though they have also been used for epidural catheters. Mann *et al*. inserted epidural catheters in 55 patients that were randomised to either a standard dressing or Biopatch®. They reported the only 2 cases of infection in patients in whom standard dressings was used, suggesting that chlorhexidine dressings may have efficacy in that context.24

There were few studies that explicitly reported adverse event data with chlorhexidine dressings, though none were experienced in a relatively small sample size. Chlorhexidine dressings appeared safe from the perspective of negligible chlorhexidine levels in the CSF.20 Overall, the risk of contact dermatitis with chlorhexidine dressings is low and reported to be 8 per 1000 in large prospective trials, which is marginally higher than standard dressings for which it is 2 per 1000.12

There were fewer organisms grown from the skin and CSF of patients treated with chlorhexidine dressings. However, not enough studies presented data on skin and CSF culture results to definitively ascertain whether chlorhexidine dressings alter the rate of skin colonisation around EVDs or the microbiological profile of associated EVDAI. Elsewhere in the body, their use has been associated with reduced colonisation in addition to reduced catheter related infections.23 Notably, although chlorhexidine dressings could reduce a source of EVDAI from skin colonisation, the possibility of microbial entry into the CSF is still a possibility from device insertion and haematogenous spread.25

There is a biological rationale for use of chlorhexidine dressings to reduce EVDAIs. Firstly, there is the observation that CSF cultures in the context of an EVDAI most commonly grow skin commensals. In a national multi-centre prospective study of EVD use in the UK skin commensals were cultured in more than half (55%) of positive cultures.2 Secondly, studies evaluating the pathophysiology of EVDAIs have found that most positive cultures occur in the context of a similar organism being cultured from skin swabs, indicative of prior colonisation. Mounier *et al*. prospectively studied 101 patients treated with antibiotic impregnated EVDs that were in place for ≥48 hours and categorised EVDAIs according to source. 10 patients had an EVDAI (10%) and of these, the commonest source identified was skin in 6 out of 10 cases, inferred from growth of the same organism in both CSF and skin.25 It is therefore reasonable to assume that a reduction of skin colonisation could reduce the rate of secondary EVDAI. This was observed in one of the included randomised studies, which showed a reduction of ~50% in both skin colonisation and EVDAI with chlorhexidine dressings.13

Limitations of this review include a high risk of bias in most included studies and significant heterogeneity in the available published data. There was only one randomised trial reported in the literature, and this was markedly underpowered. The included case series did not attempt to control for confounding variables, although treatment protocols including chlorhexidine dressings were associated with a significantly lower risk of EVDAI. The actual type of chlorhexidine dressing used with EVDs (standard or Biopatch®) also varied between studies and there was no available comparison data. Most included studies did not report safety data associated with chlorhexidine dressing use. Finally, all of the included literature related to adults, which could be due to safety concerns of chlorhexidine dressings in the pediatric age group.26

**Conclusion**

This systematic review and meta-analysis found limited quality evidence evaluating the efficacy of chlorhexidine dressings in the context of EVDAI. Although the chlorhexidine dressing group had a significantly lower incidence of EVDAI, existing studies had high levels of bias. There is a clinical need for future adequately powered randomised trials to definitively evaluate the safety and efficacy of chlorhexidine dressings for EVDs.

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**Table 1. Study characteristics and EVD protocols**. \*Note that additional interventions were also used alongside chlorhexidine dressings. These were controlled between the treatment arms in only one study (Roethlisberger 2018). Abbreviations: CHG = chlorhexidine; Y = yes; N = no.

|  |  |
| --- | --- |
|  | **Included studies** |
| **Flint 2013** 21 | **Scheithauer  2014 20** | **Roethlisberger 2018** 13 | **Sieg 2018** 18 | **Darrow 2018** 19 |
| **Study design** | Case series(before/after protocol) | Case series(no control group) | Randomised controlled trial | Case series(before/after protocol) | Case series(before/after protocol) |
| **Dressing type evaluated** | Biopatch® | Generic CHG | Generic CHG | Biopatch® | Biopatch® |
| **Additional interventions\*** | **Prophylactic pre-procedural antibiotics** | Y | NR | Y | N | Y |
| **Wide hair removal** | Y | NR | Y | Y | Y |
| **Skin prep** | Y - CHG | NR | Y | Y | Y |
| **Strict aseptic technique** | Y | NR | Y | Y | Y |
| **Catheter type** | Antibiotic | NR | Silver | Antibiotic | Antibiotic |
| **Catheter tunnelled ≥5cm** | 3-5cm | NR | Y | Y | Y |
| **Routine dressing change** | N | NR | Y | N | N |
| **Post-procedure antibiotics** | N | NR | N | N | N |
| **Strict aseptic handling post-procedure** | Y | NR | N | N | N |
| **Routine sampling** | N | NR | Y | N | Y |

**Table 2. The rate of EVDAI compared between study arms**. Abbreviations: EVDAI = EVD associated infection; NR = not reported; N = number of patients; SAH = subarachnoid haemorrhage; ICH = intracranial haemorrhage; IVH = intraventricular haemorrhage; TBI = traumatic brain injury.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Design** | **Group** | **Total N** | **Mean age (range)** | **Pathology** | **EVD type** | **Mean duration of EVD (range)** | **EVDAI****N (%)** |
| Roethlisberger 2018 13 | Randomised controlled trial | Generic chlorhexidine | 28 | 58(52-71) | SAH: 15 (54%)ICH/IVH: 12 (43%)Tumour: NRTBI: NR | Silver | 8 (5-10) | 4 (14.3%) |
| Non-chlorhexidine dressing | 27 | 60(46-63) | SAH: 20 (74%)ICH/IVH: 5 (19%)Tumour: NRTBI: NR | Silver | 10 (6-12) | 9 (33.3%) |
| Sieg 2018 18 | Case series (before/after protocol) | Biopatch® (after protocol) | 184 | NR | NR | Antibiotic | NR | 0 (0.0%) |
| Before protocol | 81 | NR | NR | NR | NR | 10 (12.3%) |
| Darrow 2018 19 | Case series (before/after protocol) | Biopatch® (after protocol) | 56 | 54 (NR) | NR | Antibiotic | 7 (NR) | 2 (3.6%) |
| Before protocol | 218 | 54 (NR) | NR | NR | 9 (NR) | 9 (4.1%) |
| Flint 2013 21 | Case series (before/after protocol) | Biopatch® (after protocol) | 143 | 61 (48-72) | SAH: 45/119 (38%)ICH/IVH: 48/119 (40%)Tumour: 10/119 (8%)TBI: 5/119 (4%) | Antibiotic | 11 (4-15) | 1 (0.7%) |
| Before protocol | 143 | 61 (50-73) | SAH: 63/143 (44%)ICH/IVH: 52/143 (36%)Tumour: 23/143 (16%)TBI: 1/143 (1%) | NR | 8 (4-12) | 9 (6.3%) |