Original Article

A Randomised Control Trial on the Use of Topical Methicillin in Reducing Post-Operative Ventriculoperitoneal Shunt Infection

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Abstract

Background: **A double-blind randomised control study was conducted on all patients who were admitted or referred to the Department of Neurosurgery, Sultanah Aminah Hospital, Johor Bahru, with a diagnosis of hydrocephalus where a ventriculoperitoneal shunt was indicated.**

Methods: **The period of study was from November 2005 to May 2007, and the follow-up period was 3 months after surgery. Randomisation was carried out in the operating room prior to the procedure. The scrub nurse selected a sealed envelope, which contained the assignment of each patient to 1 of 2 treatment groups: Group 1 patients were treated with topical methicillin, and Group 2 patients were not treated with topical methicillin. Prophylactic antibiotic, cefuroxime (25 mg/kg) was given intravenously at induction. Standard sterile operative technique was followed in preparing and draping the patients.**

Results: **A total of 90 patients were recruited in the study, and 13 (14.4%) patients developed an infection within 3 months post-operation. Group 1 had a 8.9% risk of infection, and Group 2 had a 20% risk; however, there was no statistically significant post-operative ventriculoperitoneal shunt (VPS) infection reduction with the use of topical methicillin in VPS surgery (P = 0.230). Multivariate analysis showed that only duration of surgery had a significant influence on the incidence of post-operative VPS infection in the non-methicillin group (P = 0.02). The non-methicillin group had an 8 times greater risk of developing post-operative VPS infection than the methicillin group if surgery lasted longer than 1 hour.**

Conclusion: **Topical methicillin had no significance in the reduction of post-operative VPS infection.**

Keywords: *methicillin, neurosurgery, post-operative wound infection, topical administration, ventriculoperitoneal shunt*

Introduction

The development of effective cerebrospinal fluid (CSF) shunts represented a landmark achievement in neurosurgery. Although shunts have improved the morbidity and mortality associated with disordered CSF mechanics over the past 30 years, they are associated with many potentially avoidable complications. Of these, post-operative infection remains a major complication (1–3). A great deal of experimental and clinical research is aimed at determining ways of preventing these infections. The problem of shunt infections nonetheless remains unsolved, and widely varying, contradictory data abound on the incidence of shunt infection (4–7).

The reported shunt infection rates range 5%–27% in South America (4) with most centres reporting an incidence 5%–20% (1). Most shunt infections occur within 2 months, and 80% within 6 months post-operation. Inoculums are believed to arise from skin organisms at the time of shunt implantation, although this is not always the case (7). Factors that are most commonly implicated in shunt infections are listed in Table 1.

The most common bacteria involved in early shunt infections are *Staphylococcus epidermidis* (52.8%–88.9%) and *Staphylococcus aureus* (12.0%–40.0%). These bacteria may enter the operative field during surgery from hair follicles and sebaceous glands opened by the surgical incision. Insufficient aseptic technique and a long-lasting surgery also contribute to this risk (7,9,10).

Table 1: Factors implicated in shunt infection (1,4,8)

Factors
Poor pre-operative skin condition
Age less than 6 months
Reinsertion of VPS after infection
Presence of wound dehiscence
Proximal versus distal revision (greater risk with proximal revision)
Presence of hydrocephalus
Time of day the operation performed (greater risk after office hours)
Number of staff in operating room
Neurosurgeon's experience
Length of operation (lower risk with shorter duration)
Presence of airborne organisms in operating room

In Malaysia, ventriculoperitoneal shunt (VPS) infection is the most common infection reported in neurosurgery. Although stringent rules have been applied, a successful reduction in infection rates in the operating rooms has not been achieved. There are certain neurosurgical centres that allow only consultants and senior registrars to perform VPS surgery; however, even this practice has not greatly decreased the infection rates (2,10,11).

The use of topical antibiotics and antibiotic-impregnated shunt systems during VPS surgery has been widely practiced (12,13). However, there is no specific study done in the local setting to evaluate the efficacy of these procedures. Methicillin is a narrow spectrum beta-lactam antibiotic of the penicillin class. It is used to treat infections caused by susceptible Gram-positive bacteria, particularly beta-lactamase-producing organisms, such as *Staphylococcus aureus*, that would otherwise be resistant to most penicillin. Topical methicillin was chosen to be tested as it is cheap and do not need any special preparation. It is used in many centres and is also quoted in VPS surgery protocol by Andrew Kaye in his textbook, Operative Neurosurgery.

The main objective of this study was to evaluate the role of methicillin as a topical antibiotic during shunt insertion in VPS surgery with the aim of reducing the rate of post-operative infection. This study also evaluated factors that could play a role in post-operative shunt infection such as gender, race, age, aetiology of hydrocephalus, surgeon's experience, duration of the surgery, and time of the surgery (during or after office hours). These analyses would be helpful for developing guidelines to prevent or reduce post-operative VPS infection.

Subjects and Methods

The study included patients of all ages, races, and genders that were either admitted or referred to the Hospital Sultanah Aminah Johor Bahru. The patients were newly diagnosed with hydrocephalus of any aetiology and needed a VPS. Patients who required a revision of a VPS were excluded in this study. Patients who had poor skin condition, were undernourished, or had preoperative Glasgow Coma Scale (GCS) of less than 13 were also excluded.

If selected patients initially had an extraventricular drain inserted and were drainage-dependent, then internalisation or VPS insertion was performed when CSF culture and sensitivity had no growth for 3 consecutive samples and CSF protein was less than 2 g/dL. Sample size was calculated at 90 with each arm of the study consisting of equal number of [patients: 45 patients treated with topical methicillin (Group 1) and 45 patients not treated with topical methicillin (Group 2). These designations were then sealed in envelopes and randomly selected immediately prior to surgery. The envelope was opened by the scrub nurse and the solution was prepared according to the group assignment, completely unknown to anyone else in the operation theatre, including the surgeon. The envelope then was re-sealed and attached with a questionnaire containing patient's details for record.

Because this study was conducted to observe whether post-operative infection rate of VPS could be reduced with topical methicillin, independent of the surgeon's experience, certain procedures had to be standardised and made easily attainable. In the operating room at induction, patients were given a single prophylactic dose of intravenous cefuroxime (25 mg/kg body weight). The scrub

nurse then prepared the solution according to the chosen envelope. If the patient was assigned to Group 1, 1 vial of 500 mg methicillin powder was diluted in 500 mL normal saline, and if the patient was assigned to Group 2, then pure normal saline solution without any antibiotic was applied.

The surgical site was then cleaned multiple times with povidone iodine, draped and covered with opsite once the povidone iodine had dried. Surgery was then carried out with minimal manipulation and handling of the shunt system before insertion; the shunt system and all instruments used in its handling were soaked in the prepared solution. A single type of shunt system, Codman Hakim non-programmable shunt (Integra Neurosciences Inc., Plainsboro, NJ) was used in all cases. After haemostasis was achieved, the surgical site was washed with the prepared solution, and the skin was closed. The patients were subsequently followed up post-operatively with clinic appointments in the 1st and 3rd month.

Data analysis was done using SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL). Cross tabulation with chi-square test was used to determine whether individual categorical independent factors were randomised fairly in each group. $P < 0.05$ was considered statistically significant for the univariate analysis.

The association between post-operative VPS infection and significant independent variables from univariate analysis was analysed with multiple logistic regression and adjusted for confounding factors to identify the most important determinant. The final model of factors using multiple logistic regression was examined for fitness using Hosmer–Lemeshow goodness-of-fit test. Each result was expressed as odds ratio (OR) and 95% confidence interval (95% CI). OR was used to assess the risk of the outcome (post-operative VPS infection) if a certain factor was present. The OR is considered significant if the 95% CI does not include OR of 1.

Results

Of the 90 patients studied, 13 (14.4%) patients developed post-operative VPS infection; 4 (8.9%) patients in the methicillin group and 9 (20 %) patients in the non-methicillin group (Table 2). The use of topical methicillin in VPS surgery did not significantly reduce post-operative infection ($\chi^2 = 2.298$, df = 1, $P = 0.23$). However, the non-methicillin group had a 2.5 times increased risk of developing post-operative shunt infection compared to the methicillin group (OR = 2.5, 95% CI = 0.73 to 9.03). This model was tested with Hosmer–Lemeshow tests where both Pearson and Hosmer–Lemeshow chi-square statistics were 0, hence, P value was 1 ($P > 0.05$). Therefore, the model fit well.

By using multiple logistic regression analysis, the forward logistic regression gave us the best model. The chi-square statistics seen in the omnibus test is significant ($P = 0.006$, df = 5) with 2 Log likelihood statistics was 57.904 at the final step. The Hosmer–Lemeshow test at df = 7 was 0.990, which is more than the conventional value (0.05); therefore, the observed number of outcomes was not significantly different from that predicted by the model. It is concluded that this model fits well. The only significant predictor of post-operative VPS infection was duration of surgery ($P = 0.02$) (Table 3). The non-methicillin group had 8 times increased risk of developing post-operative VPS infection than the methicillin group in surgery that lasted longer than 1 hour (OR = 7.73, 95% CI = 1.34 to 44.78).

No significant correlation was observed between post-operative VPS infection and demographic factors, i.e., gender, race, and age (Table 4). Similarly, none of the analysed clinical factors are significant predictors of VPS infection, except for the duration of surgery in the non-methicillin group (OR= 2.56, 95% CI = 0.73 to 9.03, $P = 0.03$) (Table 5).

Table 2: Univariate analysis between Group 1 (methicillin) and Group 2 (non-methicillin)

Factors	Non-infected *n* (%)	Infected *n* (%)	*P* value	OR (95% CI)
Use of topical methicillin				
With (Group 1)	41 (91.1)	4 (8.9)	0.23 [a]	2.56
Without (Group 2)	36 (80.0)	9 (20.0)		(0.73 to 9.03)

[a] Chi-square test

Table 3: Significant predictor from multivariate analysis on determining post-operative VPS infection

Factors	*P* value	OR (95% CI)
Duration of surgery	0.02	7.73 (1.33 to 44.78)

Table 4: Univariate analysis of demographic factors that influence post-operative ventriculoperitoneal shunt surgery in both randomised groups (Group 1: methicillin, Group 2: non-methicillin)

Factors	Non-infected *n* (%)		Infected *n* (%)		*P* value	OR (95% CI)
Gender						
Group 1						
Male	22	(48.9)	2	(4.4)	0.64 [a]	1.16
Famale	19	(42.2)	2	(4.4)		(0.12 to 9.03)
Group 2						
Male	15	(33.3)	3	(6.7)	0.48 [a]	1.43
Famale	21	(46.7)	6	(13.3)		(0.31 to 6.64)
Race						
Group 1						
Malay	29	(64.4)	4	(8.9)		
Chinese	8	(17.8)	0		0.45 [a]	-
Indian	4	(8.9)	0			
Group 2						
Malay	25	(55.6)	8	(17.8)		
Chinese	4	(8.9)	0		0.44 [a]	-
Indian	7	(15.6)	1	(2.2)		
Age						
Group 1						
Neonate	8	(17.8)	0			
Infant	4	(8.9)	2	(4.4)		
Child	6	(13.3)	0		0.12 [a]	2.8
Adult	23	(51.1)	2	(4.4)		(0.51 to 15.38)
Group 2						
Neonate	3	(0.7)	1	(2.2)		
Infant	4	(8.9)	3	(6.7)		
Child	2	(4.4)	0		0.36 [a]	1.28
Adult	27	(60.0)	5	(11.1)		(0.17 to 9.97)

[a] Chi-square test

Table 5: Univariate analysis of clinical factors that influence post-operative ventriculoperitoneal shunt surgery in both randomised groups (Group 1: methicillin, Group 2: non-methicillin)

Factors	Non-infected *n* (%)	Infected *n* (%)	*P* value	OR (95% CI)
Timing of surgery				
Group 1				
Office hours	23 (51.1)	2 (4.4)	0.60 [b]	2.86 (0.27 to 29.80)
After office hours	18 (40)	2 (4.4)		
Group 2				
Office hours	16 (35.6)	2 (4.4)	0.204 [b]	-
After office hours	20 (44.4)	7 (15.6)		
Duration of surgery				
Group 1				
< 1 hour	20 (44.4)	1 (2.2)	0.36 [b]	-
> 1 hour	21 (46.7)	3 (6.7)		
Group 2				
< 1 hour	19 (42.2)	1 (2.2)	0.03 [b*]	2.56 (0.73 to 9.03)
> 1 hour	17 (37.8)	8 (17.8)		
Aetiology				
Group 1				
Congenital	17 (37.8)	1 (2.2)	0.37 [a]	-
Tumour	15 (33.3)	2 (4.4)		
Trauma	4 (8.9)	0		
Vascular	1 (2.2)	0 (2.2)		
Infection	1 (2.2)	1		
Others	3 (6.7)	0		
Group 2				
Congenital	6 (13.3)	2 (4.4)	0.17 [a]	-
Tumour	14 (31.1)	7 (15.6)		
Trauma	1 (2.2)	0		
Vascular	9 (20.0)	0		
Infection	6 (13.3)	0		
Others	0	0		
Surgeon's criteria				
Group 1				
Consultant	2 (4.4)	0	0.23 [a]	-
Surgeon	1 (2.2)	1 (2.2)		
Registrar	4 (8.9)	0		
Trainee	13 (28.9)	2 (4.4)		
Medical officer	21 (46.7)	1 (2.2)		
Group 2				
Consultant	0	0	0.78 [a]	-
Surgeon	1 (2.2)	0		
Registrar	4 (8.9)	0		
Trainee	13 (28.9)	6 (13.3)		
Medical officer	21 (46.7)	3 (6.7)		

a Chi-square test, b Fisher's exact test
* Significant at $P < 0.05$

Discussion

This was a double-blind prospective randomised control study that involved a total of 90 patients admitted to the Department of Neurosurgery, Hospital Sultanah Aminah Johor Bahru from November 2005 to May 2007. In the randomisation of the patients, certain predictors had the disadvantage of not being uniformly randomised; these were primarily the aetiology of hydrocephalus and surgeon's status. This naturally would influence the outcome, as both of these factors influence post-operative infection rate. Aetiology as an influencing factor has been reported by Vinchon et al. They concluded that age below 4 months at shunt insertion, myelomeningocele, and post-hemorrhagic hydrocephalus were significantly correlated with post-operative shunt infection (6). Cochrane and Kestle reported that the surgeon's operative experience is an important factor in determining post-operative shunt infections (14).

There were almost an equal number of male and female patients in this study with a slight preponderance towards female patients (53.3%). No specific study has shown any influence of gender on VPS infection. Race had no significant impact on post-operative VPS infection. It was not surprising that a major group of the patients studied were from the neonate age group (12 out of 90 patients, 13.3%). This was easily explained because one of the common causes of hydrocephalus is congenital hydrocephalus, which is most often diagnosed at birth and often requires VPS insertion early in life. Neonates and infants were at high risk of developing post-operative shunt infections (13); this is attributed to an immature immune system and to surgical technique (15). Therefore, many studies on VPS infection concentrated in the paediatric age group. As stated earlier, the literature shows that subgaleal collections due to large burr holes and thin dura cause CSF leakage and increase VPS infection. Bruinsma et al. showed that prematurity is an important risk factor for ventricular catheter reservoir and ventriculoperitoneal drain-related infections, especially for patients with a gestational age of less than 37 weeks at their initial shunt placement and an extremely low birth weight (16). In this study, surprisingly, there was only 1 neonate who developed post-operative VPS infection, and the neonate belonged to the non-methicillin group. This is most likely due to awareness among surgeons of the higher risk of infection, which encourages them to be more compliant to strict sterile technique. Recently, a study in Japan showed that clinical outcome was significantly better in full-term patients who underwent early shunt placement than in those who underwent late shunt placement (17). This clearly explains the lower infection rate in the neonate group (2.2%) and the slightly higher infection rate in the infant group (11.1%). Adults accounted for 62.2% VPS placement, mainly due to obstructive hydrocephalus secondary to tumour.

Aetiology of hydrocephalus was not a risk factor in VPS infection although there are contradictory findings reported in the literature. There are studies in the paediatric age group where aetiology showed no effect on VPS infection (4,5); however, recent studies reported that the most common aetiologies of hydrocephalus in shunt-infected patients were congenital hydrocephalus-myelomeningocele, 32%, and meningitis, 23% (10,18).

Although most studies report that VPS is usually done in emergency situations, there were a similar number of emergent and non-emergent VPS cases in this study. This is most likely due to the protocol taken by both the neurosurgery and anaesthesia departments at Hospital Sultanah Aminah to have shunt surgery performed as the first case of the day to maximise the sterility of the operating room. This has been repeatedly suggested as a measure to reduce post-operative VPS infection in many literature reviews (8,19). Timing of surgery was not a risk factor for VPS infection; however, the duration of surgery was. Surgery that took longer than 1 hour in this study was associated with a significant increase in VPS infection as concluded in the multivariate analysis. It was the single most significant confounder that influenced the post-operative VPS infection and increased the odds 8 times in the non-methicillin group. The duration of surgery and the surgeon's experience are correlated; the more experienced the surgeon, the shorter the duration of the surgery. Cochrane conducted a 12-year review of the relationship between the surgeon's experience, as measured by operative volume, and the outcomes of ventricular shunt treatment of hydrocephalus in children. The 6-month shunt failure risk for less experienced surgeons was 38%, compared to 31% for more experienced surgeons. The infection rate for initial shunt insertions was 7% for patients treated by more experienced surgeons and 9.4% for those treated by less experienced surgeons. The review showed a relationship between surgeon's experience and shunt outcome, which appears to be based on the operative experience that a surgeon brings to a procedure (14).

This study could not determine whether the shunt system had an influence on post-operative VPS infection because the same standard VPS system, the Codman-Hakim shunt system (Integra Neuroscience Inc., Plainsboro, NJ), was used in all cases to decrease confounding factors that might affect the outcome of the surgery.

The infection rate with the use of topical methicillin in this study was 8.9%, and the infection rate without the use of topical methicillin was 20%. Statistically, topical methicillin did not reduce post-operative VPS infection (P = 0.230). This study is comparable to a study done by Choskey and Malik in Coventry that showed a statistically significant reduction in post-operative shunt infection rates from 15.56% to 0.33% with the use of topical and intrathecal vancomycin. In their study, betadine was instilled into the exposed subcutaneous area, and intrathecal vancomycin was injected when the ventricular catheter was inserted. Even though this was a prospective study and did not have a placebo, most of the confounding factors in increasing the risk of infection were eradicated. Only a single experienced surgeon was employed in this study, surgery was done as the first case of the day, and staff in the operating room was limited to 4 personnel (1). In the current study, only topical methicillin was used; no intrathecal drugs were used because their efficacy is not fully proven in the literature and no intrathecal preparation is available in Malaysia. A placebo was used in this study; however, the confounding factors into both groups cannot be controlled. This might be influenced by the fact that there were many surgeons involved and different aetiologies of hydrocephalus. However, the main objective was to observe whether topical methicillin could reduce post-operative VPS infection rates regardless of the confounding factors. Thus, it can be clearly concluded that topical methicillin has no significant effect in reducing post-operative VPS infection.

The univariate analysis revealed that only duration of surgery in the non-methicillin group was a significant factor in determining post-operative VPS infection (P = 0.03). This was also revealed in the multivariate analysis where duration of surgery in the non-methicillin group remained as the significant factor in the model (P = 0.02).

However, this randomised study is not definitive because the results do not support the hypothesis that topical methicillin would reduce post-operative VPS infection. This could be due to the small sample size and the study being conducted in a single centre with a short follow-up period of 3 months. Therefore, a further multicentre, randomised control trial on a new sample size based on the infection range of this study could support the hypothesis. Where $P1 = 8.9$ and $P2 = 20$, $\alpha = 0.05$, and $\beta = 0.2$, thus sample size should be 100 for each group. Study follow-up should be extended to at least 6 months because several studies have shown 80 % of shunt infections occurs in the first 6 months (20,21).

Conclusion

This study showed that there was reduced post-operative VPS infection in VPS surgery using topical methicillin, compared with VPS surgery with no topical methicillin. However, the results were not statistically significant. Thus, this concludes that the use of topical methicillin does not reduce post-operative VPS infection. The results obtained might be influenced by some factors that were not equally distributed in each group.

It seems that long duration of surgery that last more than 1 hour, when not using topical methicillin, imposed a significant risk for the development of post-operative VPS infection.

Authors' Contributions

Conception and design, critical revision of the article, final approval of the article, administrative, technical, or logistic support: JSA
Obtaining of funding, provision of study materials or patients, collection and assembly of data, statistical expertise, analysis and interpretation of the data, drafting of the article: SCT

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