Original Article
http://mjiri.iums.ac.ir

Medical Journal of the Islamic Republic of Iran (MJIRI)
Iran University of Medical Sciences

Is Taurolidine-citrate an effective and cost-effective hemodialysis catheter lock solution? A systematic review and cost- effectiveness analysis

Zahra Kavosi[1], Maryam Sarikhani Khorrami[2], Khosro Keshavarz[3], Abdosaleh Jafari[4]
Amir Hashemi Meshkini[5], Hamid Reza Safaei[6], Shekoufeh Nikfar*[7]

Received: 14 September 2015 Accepted: 15 November 2015 Published: 2 April 2016

Abstract

Background: Prevention of catheter-related infection is of prime importance,. However, because of the risks caused by the leakage of circulating antibiotics and development of resistance to antibiotics, they are replaced by lock solutions. The aim of this study was to evaluate the efficacy and cost- effectiveness of taurolidine-citrate as a hemodialysis catheter lock solution compared to other common alternatives in Iran.

Methods: To evaluate the efficacy of taurolidine-citrate, a systematic review was conducted by searching electronic databases. The outcomes of interest for cost-effectiveness analysis were as follows: "Catheter-related bacteremia episodes"; "catheter-related bacteremia-free survival"; "catheter thrombosis rate" for efficacy evaluation and "reduction of catheter-related infection". For evidence synthesis, a meta-analysis was conducted on the extracted efficacy data. To evaluate the cost of treatments, direct medical costs were included, and the incremental cost-effectiveness ratio was calculated for each comparison. The payers' (patients and insurance companies) perspectives were used for cost analysis.

Results: After carrying out the systematic process, three articles were included in the analysis. Considering 95% confidence interval, the relative difference was -0.16 (-0.25 to -0.07) for catheter-related bacteremia episode, indicating that the rate of catheter-related infections in hemodialysis patients who used taurolidine-citrate was 16% less than in those hemodialysis patients who received heparin. Considering 95% confidence interval, the relative difference was 0.13 (-0.06 0.32) for catheter thrombosis, showing that the rate of catheter-related thrombosis in hemodialysis patients who used taurolidine-citrate was 13% more than in hemodialysis patients who received heparin. The results of this analysis indicated that taurolidine-citrate, compared to heparin, was more effective in preventing catheter-related infection; therefore, it could be considered as a superior strategy. Nevertheless, compared to heparin-gentamicin combination, taurolidine-citrate is an inferior strategy because of its higher cost and lower infection prevention.

Conclusion: Compared to heparin, taurolidine-citrate is a superior option, but it is an inferior strategy compared to heparin-gentamicin combination. The clinical evidences on taurolidine-citrate, heparin and gentamicin/heparin are not sufficient for making confident decisions.

Keywords: Taurolidine-Citrate, Taurolock, Health Technology Assessment, Cost-effectiveness.

Cite this article as: Kavosi Z, Sarikhani Khorrami M, Keshavarz Kh, Jafari A, Hashemi Meshkini A, Safaei HR, Nikfar Sh. Is Taurolidine-citrate an effective and cost-effective hemodialy-sis catheter lock solution? A systematic review and cost- effec-tiveness analysis. *Med J Islam Repub Iran* 2016 (2 April). Vol. 30:347.

[1]. PhD Health Service Management, Associate Professor, Health Human Resource Research Center, School of Management and Medical Information, Shiraz University of Medical Sciences, Shiraz, Iran. zhr.kavosi@gmail.com
[2]. MSc of Health Economics, Student Research Committee, School of Management and Medical Information, Shiraz University of Medical Sciences, Shiraz, Iran. maryamsarikhani@yahoo.com
[3]. PhD of Pharmacoeconomics and Pharmaceutical Administration, Assistant Professor, Department of Health Economic and Health Human Resource Research Center, School of Management and Medical Information, Shiraz University of Medical Sciences, Shiraz, Iran. khkeshavarz2007@gmail.com
[4]. PhD student of Health Economics, Health Human Resource Research Center, School of Management and Medical Information, Shiraz University of Medical Sciences, Shiraz, Iran. abdosaleh.jafari@gmail.com
[5]. PhD in Pharmacoeconomics & Pharmaceutical Administration, Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. amirhashemi82@gmail.com
[6]. MD, Assistant Professor, Department of Nephrology, Aja University of Medical Sciences, Tehran, Iran. Dr_hamid.safaei@yahoo.com
[7]. (**Corresponding author**) PharmD, PhD of Pharmacoeconomics and Pharmaceutical Administration, Associate Professor, Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of medical Sciences, Tehran, Iran. nikfarsh@tums.ac.ir

Introduction

End-stage renal disease (ESRD) is a clinical condition with uremic syndrome which has a very poor prognosis for patients (1). It is one of the most important life-threatening diseases in the world, incurring considerable social and economic burden on patients, their families and society (2). Patients with ESRD need medical intervention as well as supportive care including hemodialysis, peritoneal dialysis, or kidney transplantation. Since many of these patients are not eligible for kidney transplantation, they should be treated via dialysis (3). Hemodialysis is the most common treatment strategy for kidney failure, for which either an arteriovenous graft, central venous catheters (CVC), arterialvenous shunted external arteriovenous fistula is used for vascular access (4).

Although the use of CVC has played an important role in modern medicine, it is an important cause of morbidity and mortality in hospitals (3). Because of the use of central catheter, catheter-related bloodstream infection (CRBSI) is one of the most common fatal complications (5). It is estimated that 200,000 cases of CRBSI occur in the U.S. and its related mortality has been approximately estimated to be about 12-25% (6). In a study on 68 children, from 2000 to 2005, in the dialysis unit of a Children's Hospital in Mashhad (Iran), the central vein catheter-related infection was reported to be about 48% (3).CRBSI increases the length of stay around 4.2 to 5.7 days, and it has an increasing trend (7).

Prevention of bacterial infection is very important (8). In addition to good clinical practices to prevent catheter-related infection, the use of the subclavian vein as the best anatomic site, and utilization of impregnating catheters with antiseptics or antibiotics could also effectively prevent potential infection (9). The benefits of using gentamicin, cephalosporins, minocycline, and a high concentration of citrate in reducing catheter-related bacteremia(CRB) rate have been reported (10). However, because of the risks related to leakage of circulating antibiotics and development of resistance to antibiotics, it is replaced by taurolidine-citrate lock solution (8). It is appropriate for short- and long-term catheter and is made of 2% taurolidine, as an anti-microbial agent (with a broad spectrum of activity against gram-positive and gram-negative organisms and fungi) and 4% citrate to prevent thrombus formation. Taurolidine-citrate is not an antibiotic and no in vitro antimicrobial resistance has been reported yet (11). Recently, it has become available in Iran, but it is not covered by health insurances because of doubts about its efficacy and cost-effectiveness compared to the current alternative (heparin).

In this study, as a part of health technology assessment (HTA) project and according to our former HTA studies (12-15), both the efficacy and cost- effectiveness of taurolidine-citrate was evaluated as a hemodialysis catheter lock solution in Iran.

Research Questions

1) What is the cost of taurolidine-citrate in Iran when used to prevent catheter-related infections in hemodialysis patients?

2) How much does heparin cost in Iran when used to prevent catheter-related infections in hemodialysis patients?

3) How much does heparin-gentamicin cost in Iran when used to prevent catheter-related infections in hemodialysis patients?

4) How much does the ICER of taurolidine-citrate cost in Iran compared to heparin in the prevention of catheter-related infections in hemodialysis patients?

5) How much does the ICER of taurolidine-citrate cost compared to heparin-gentamicin in the prevention of catheter-related infections in hemodialysis patients in Iran?

Study Objectives

1) According to the systematic review, taurolidine-citrate is safer than heparin in the prevention of catheter-related infections in hemodialysis patients.

2) According to the systematic review, taurolidine-citrate is safer than heparin-gentamicin in the prevention of catheter-related infections in hemodialysis patients.

3) According to the systematic review, taurolidine-citrate is more cost effective than heparin in the prevention of catheter-related infections in hemodialysis patients.

4) According to the systematic review, taurolidine-citrate is more cost effective than heparin-gentamicin in preventing catheter-related infections in hemodialysis patients.

Methods

1) Systematic Review

Data Sources: To evaluate the efficacy of taurolidine solution lock, a systematic review was conducted through searching studies published from 1996 to the end of 2013 in electronic databases including PubMed, ISI Web of Science, Scopus, and Cochrane review database. The keywords used were as follows: ″Taurolidine″; "taurolidine-citrate"; ″taurolock″ "catheter-related Infection"; "catheter-related sepsis" and″hemodialysis″.

Population: Hemodialysis Patients

Intervention: Taurolidine-Citrate

Comparators: Heparin and Heparin-Gentamicin

Outcomes: Studies were included in the clinical review if they reported primary data on one or more of the following outcomes: “CRB episode”, which is defined as the percentage of patients with bacterial infection due to the catheter; “CRB-free survival”, which is defined as the cumulative survival rate without bacterial infection related to catheters in 90 days; and “catheter thrombosis rate”, which is defined as the incidence rate of catheter thrombosis.

Inclusion Criteria: Studies were considered eligible for inclusion if they met the following criteria:

Study Design: The published articles had to be written in English, utilized randomized controlled trials (RCTs) method, meta-analysis and economic evaluation, and had to directly evaluate the clinical efficacy of taurolidine-citrate compared to alternatives. In other words, the studies focused on the following question: "Does taurolidine-citrate reduce the catheter-related infections and thrombosis, compared to heparin and heparin-gentamicin, in the hemodialysis patients?"

Exclusion Criteria: All in vivo and animal studies, uncontrolled, observational, and biochemical effects studies and A Jadad score of less than 3 were excluded.

Data extraction: Two authors separately examined the results of our systematic search through reviewing the titles and abstracts and eliminated duplicates and unrelated reports and those meeting the exclusion criteria. Then the reports selected by the authors were rechecked to make a decision about including them in the study. In the next step, the full texts of the remaining articles were assessed to evaluate the inclusion and exclusion criteria in each of them and to select the final studies.

Assessment of the Trial Quality: The methodological quality of all included studies was evaluated by the Jadad score, assigning a score of 0 to 5 to each study based on randomization, blinding and dropouts (withdrawal). The score of two was given to the study if appropriate methods of randomization was described, the score of one was assigned to those studies , which were merely described as ‘randomized’, and the score of zero was given when no details were provided to evaluate randomization. Two points can be given for blinding in the study: A score of two were allocated if patients and investigators were made blind by appropriate methods; the score of one was given if the study was described merely as double blind; and the score of zero was allotted if details about blinding were not provided. The third item to be scored was the reporting of withdrawals. The study received a score of one if all patients were accounted for in the analysis, and reasons for withdrawals were provided. A score of zero was given when information regarding withdrawals was incomplete. In this method, scores ≥ 3 were con-

sidered as acceptable in terms of quality. A Jadad score of less than 3 was considered as an exclusion criterion (13).

2) Evidence Synthesis

Statistical Analysis: Data were extracted and formed in 2 × 2 tables by study characteristics and were analyzed using Stata software version 2.7.9. Relative differences (RD) and 95% confidence intervals (95% CI) were calculated using Mantel-Haenszel, Greenland-Robins (for fixed effects) or Der Simonian-Laird (for random effects) methods. The Cochran Q test was used to test heterogeneity, and $p< 0.05$ was considered statistically significant. In case of heterogeneity or insufficiency of the included studies, the random effects model was used. Funnel plot was used as a publication bias indicator. Clinical importance was evaluated by the Edwards-Nunnally method.

3) Cost-effectiveness Analysis

The model was structured as an initial decision tree, in which hemodialysis patients entered at the initiation of the treatment, and received taurolidine-citrate or heparin or heparin-gentamicin. Followed by the subtree for each strategy option, the condition was followed through treatment, including any number of possible outcomes. At each terminal node, values for cost and effectiveness were associated with that outcome. Probabilities of the subtree in the decision tree model were obtained from the studies. A time frame of 3 months was considered.

Effectiveness Analysis: The outcome of interest in this cost-effectiveness study was "reduction of catheter-related infection". The results of meta-analysis were used to extract the probability of experiencing at least one infection during three months. The probabilities of CRB and re-catheterization after using antibiotics was also extracted from Filiopoulos and TvanaiiSani´s studies (10,16).

Cost: To estimate the costs associated with taurolidine and alternatives, we consulted a group of nephrology specialists. In this study, direct medical costs, including the costs of catheter, taurolidine, heparin, and gentamicin, antibiotics, hospitalization, etc. were included in the analysis. The payer's (patients and insurer) perspectives were used for cost analysis. To exchange the prices from Iranian Rials (IRR) to US Dollars (USD), we used the exchange rate announced by the Central Bank in 2014, which was 26,670 Rials per Dollar. A hypothetical cohort of 1,000 people was used to run the model and probabilities obtained from the studies.

Incremental Cost-Effectiveness Ratio (ICER): ICER was calculated based on the results of the effectiveness and cost of each of the three mentioned drugs (taurolidine-citrate, heparin, and gentamicin-heparin).

Sensitivity Analysis: To test the robustness of our results, a sensitivity analysis was carried out by considering the uncertainty of the key parameters. The one-way sensitivity analysis was performed, and the value of each variable was increased by 20%; a tornado diagram was used to present the results.

Results

After the initial search, 1,157 articles were identified including 231 articles from PubMed, 647 from Scopus, 235 from ISI, and 44 from Cochrane. After carrying out the systematic process on the searched studies with regards to the inclusion and exclusion criteria, only three articles were recognized as suitable for analysis (8,10,17). The full process of the study selection is demonstrated in Fig. 1. All three studies were randomized clinical trials, in which the efficacies of these drugs were reported. A summary of the selected studies about alternatives, dose prescription and the number of patients is listed in Table 1. Jadad Score of all studies were 3 or higher, so we included all of them in the final analysis.

The selected studies were assessed for three outcomes including: "CRB episode", "CRB-free catheter survival" and "catheter thrombosis rate". Based on these outcomes, the results of the three studies were extracted (Table 1).

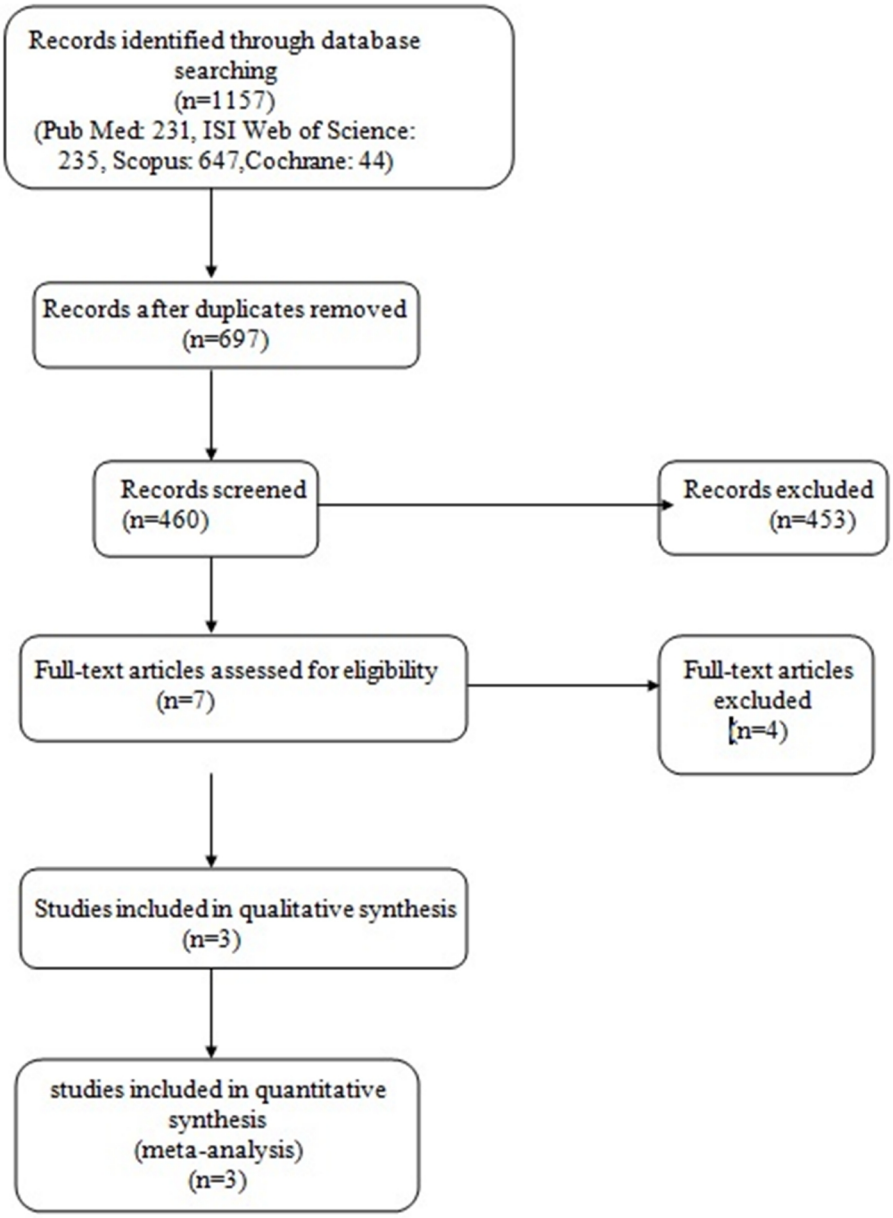

Fig. 1. Search Algorithm of the Articles. PRISMA format. N = number of articles

CRB Episode: The outcome of CRB episode was investigated in all studies. According to Table 1, CRB episode was 12.14% (17/140) in taurolidine-citrate group and 28.57% (40/140) in the heparin group. The result of meta-analysis revealed that, with 95% confidence interval, the risk difference for CRB episode was -0.16 (-0.25 to -0.07), (Fig. 2). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous (p= 0.71) and could be combined. However, the random effects for individual and summary for RD was applied due to the small number of the studies included in the review. Publication bias for "CRB" in patients, among taurolidine versus alternative therapies, could not be evaluated due to the very few strata.

Catheter Thrombosis Rate: The outcomes of catheter thrombosis were determined in two studies (8,10). Catheter thrombosis rate was 14.28% (20/140) in taurolidine-citrate group and 26.42% (37/140) in the heparin group. The meta-analysis showed a risk difference of l0.13 (-0.06-0.32) for CRB episode, with 95% confidence interval (Fig. 3).

Table 1. Characteristics of the Selected Studies in the Systematic Review and Effectiveness of Heparin and Taurolidine-Citrate Based on Three Outcomes

Study	Arms of study	Number of patients	Average of Patients Age	Dose & Route of Treatment	Effectiveness		
					CRB eEpisode (Incidence n(%))	CRB-Free Catheter Survival (cumulative CRB-free catheter survival at 90 days)	Catheter Thrombosis rate N (%)
Filiopoulos V, et al., 2011	(A): Gentamicin/heparin-(B): Taurolidine/citrate (C): Heparin	60-59-58	(A): 72 (50–80) (B): 75 (36–95) (C): 70 (42–84)	(A): 40 mg/ml gentamicin and 5,000 U/ml unfractionated heparin; ratio 1:3 (B):1.35% taurolidine and 4% sodium citrate; TauroLock TM , TauroPharm GmbH (c): heparin 5,000 U/ml	(A): 6(10%); (B): 8(13.5%) (C): 20(34.48) ********** (A) vs (C): χ^2= 6.62, p= 0.01 (B) vs (C): χ^2= 4.34, p= 0.03. (A) vs (B): N sig	(A): 82% (B): 78% (C): 26% ********** (A) vs (C): log-rank 3.03, p= 0.002 (B) vs (c):log-rank 2.63, p= 0.008 (A) vs (B): N sig	(A): 11 (14.86%) (B): 9 (11.84%) (C): 6 (8.95%) ********** A) vs (B):χ^2= 0.23, p= 0.63: N sig (A) vs (C): χ^2= 0.91, p= 0.33: N sig (B) vs (c):χ^2= 0.26, p= 0.61: N sig
Solomon LR, et al., 2010	(A): Taurolidine/citrate (B): Heparin	53-54	(A): 59.8±14.7 (B): 56.7±17.4	(A):1.35% taurolidine and 4% citrate (B): Heparin (5,000 U/mL)	(A):9 (17%) (B): 16 (30%) ********** p=0.1: (A) vs (B): N sig	Not reported	(A): 28 (53%) (B): 14 (26%) ********** p= 0.006; significant
Betjes MGH, et al., 2004	(A): Taurolidine/citrate (B): Heparin	28-28	(A): 58.3±16.3 (B): 50.3±20.4	(A):1.35% taurolidine and 4% citrate; (B): Heparin (5,000 U/mL)	(A):0 (B): 4 (14%) ********** p= not reported	the sepsis-free survival was significantly lower in patients [B] compared with [A] group (p= 0.047)	Not reported

The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous (p= 0.08) and could be combined. However, the random effects for individual and summary for RD was applied due to the very few included studies. Moreover, publication bias for the included studies could not be evaluated between taurolidine and alternative therapies in patients due to the very few strata.

Cost-Effectiveness Analysis: In this study, direct medical costs including the costs of catheter, taurolidine-citrate, heparin and gentamicin, antibiotics, hospitalization, etc. were included in the analysis. A decision tree model was used (Fig. 4), and the probabilities of the decision tree model were obtained from the available evidences (Table 2). Moreover, the overall cost per 1,000 populations was calculated using the decision tree model. Also, prevention of catheter-related infection was considered as the outcome, which was obtained from previous studies (10).

The total direct cost of taurolidine-citrate was $236,697 and the cost of heparin and heparin/gentamicin was $162,088.1 and $37,750.68, respectively. In addition, the effectiveness of taurolidine-citrate, heparin and heparin/gentamicin was 780, 260 and 820 CRB free patients, respectively (Table 3).

Table 2. Probability of CRB Free, CRB and Re Catheterization

Probabilities	Re catheterization	CRB	CRB free
Taurolidine-citrate	0.33	0.22	0.78
Heparin	0.33	0.74	0.26
Heparin-gentamicine	0.33	0.18	0.82

Table 3. The Cost and Effectiveness of Taurolidine-Citrate, Heparin, and Gentamicin/Heparin

Drugs	Total cost	effectiveness	ICER (versus Heparin)	ICER (versus Heparin/gentamicin)	ICER (versus taurolidine citrate)
Taurolidine-citrate	236697.4	780	143.48	-4973.67	NA
Heparin	162088.1	260	NA	Not calculated	143.48
Heparin-gentamicin	37750.68	820	Not calculated	NA	-4973.67

The ICER was calculated to compare taurolidine-citrate locks solution with both heparin and heparin-gentamicin combination. The results of this analysis indicated that the ICER for taurolidine-citrate and heparin was estimated to be $143.8, so in order to make decisions it should be compared with a threshold. The recommendation of the World Health Organization was considered as the threshold, in which the ICER between one to three times of the GDP per capita is considered as cost-effective, but the ICER of more than three times is not cost-effective (18). Based on the report of the central bank of Iran, the GDP was 4,670 Dollars in 2014, three times of which is 14,010 Dollars. Considering that the ICER is $143.8 and it is lower than this threshold, taurolidine-citrate is more cost-effective and a superior strategy compared to heparin. Nevertheless, compared to heparin-gentamicin combination, taurolidine-citrate is an inferior strategy due to its higher cost and lower infection prevention. The ICER for taurolidine-citrate and heparin-gentamicin was estimated -4,973.67 USD.

Sensitivity Analysis: To test the robustness of our results, we conducted a sensitivity analysis by considering the uncertainty of the key parameters. The one-way sensitivity analysis was performed and the value of each variable was increased by 20%; the results were presented using a tornado diagram. Tornado diagram for taurolidine-citrate, indicated that cost-effectiveness

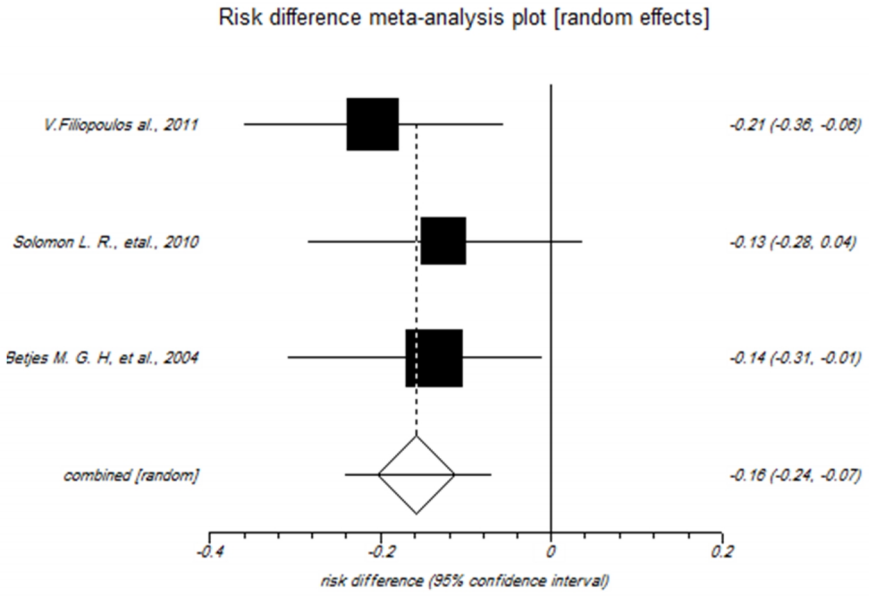

Fig. 2. Individual and Pooled Risk Difference for the Outcome of "CRB Episode" in the Studies Considering Taurolidine-Citrate comparing to Heparin Therapy

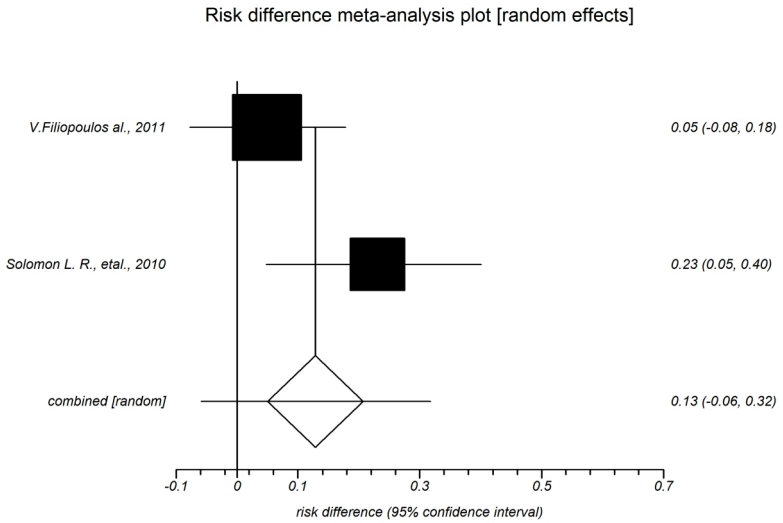

Fig. 3. Individual and Pooled Risk Difference for the Outcome of "Catheter Thrombosis Rate" in the Studies Considering Taurolidine-Citrate Comparing to Heparin Therapy

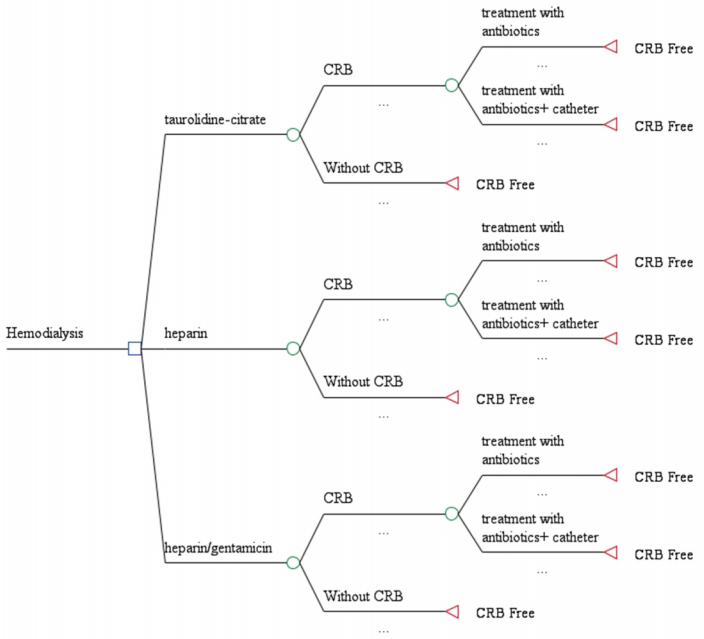

Fig. 4. Decision Tree Model to Estimate Longer Effectiveness and Cost Analysis

ratio was most sensitive to the effectiveness of taurolidine-citrate, and least sensitive to the cost of taurolidine-citrate compared to heparin, (Fig. 5). Moreover, tornado diagram for taurolidine-citrate comparing heparin-gentamicin indicated that cost-effectiveness ratio was most sensitive to the effectiveness of taurolidine-citrate. In addition, the ICER compared to the 20% increase in the cost of heparin-gentamicin, is very robust and its effect is not shown in the diagram (Fig. 6).

Discussion

According to the results of the meta-analysis and based on the outcome of the "rate of catheter-related thrombosis", there was no statistically significant difference between the levels of effectiveness of taurolidine-citrate and heparin. This study also revealed that taurolidine-citrate was a superior option compared to heparin and an inferior strategy (higher cost and lower efficacy) compared to heparin-gentamicin combination.

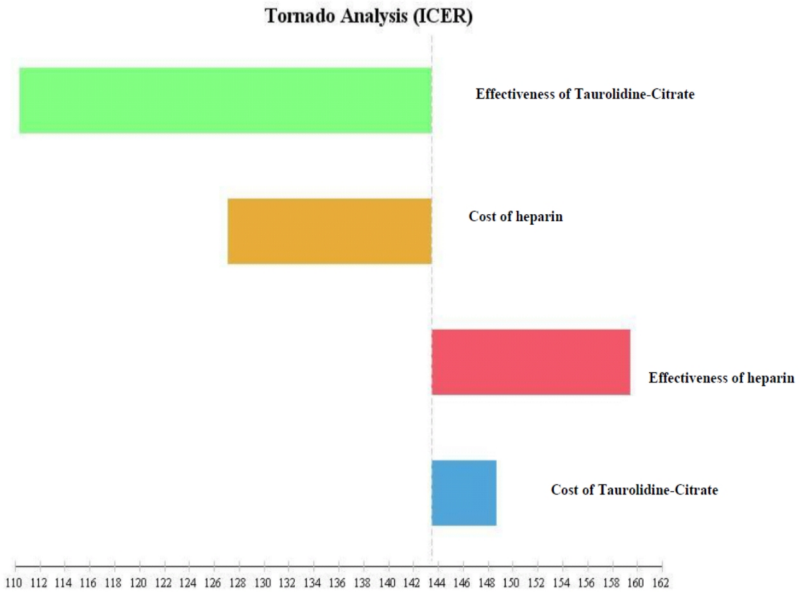

Fig. 5. Tornado Graphs of Sensitivity Analyses for the Taurolidine-Citrate Compared to Heparin

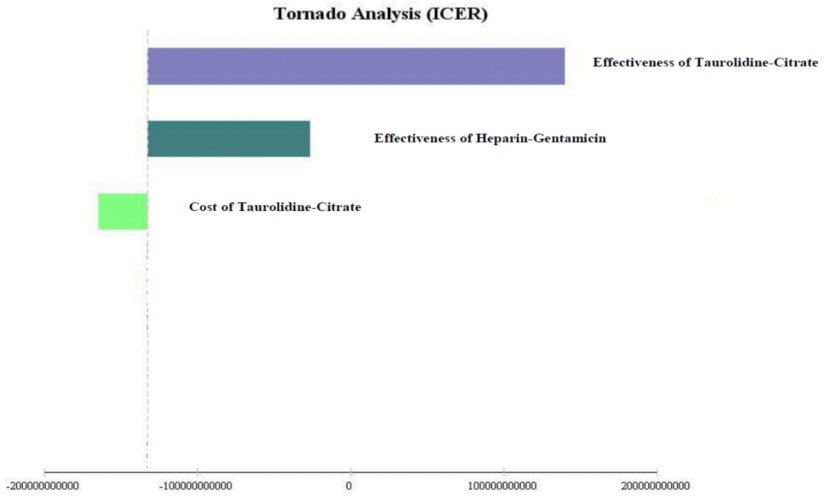

Fig. 6. Tornado Graphs of Sensitivity Analyses for the Taurolidine-Citrate Compared to Heparin-Gentamicin

Filiopoulos et al. (10) in their study, found that the rate of CRBSI in taurolidine-citrate was significantly lower than heparin (p=0.03), but the rate of CRBSI was higher in taurolidine-citrate group in terms of prevention of thrombosis; however, it was not statistically significant (p= 0.61). Overall, when heparin is used in combination with antibiotics, CRBSI rate will become lower compared to taurolidine-citrate, but the difference is not statistically significant, meaning that the heparin-antibiotic can be more effective than taurolidine-citrate. On the other hand, taurolidine-citrate does not cause bacterial resistance (19) and this can be an advantage for taurolidine-citrate. In an observational study (20), Solomon et al. showed that the amount of bacteria after using taurolidine-citrate-heparin, taurolidine-citrate, and heparin was 1.33,1.22, and 3.25 per 1,000 catheter days, respectively. Moreover, adding 500 ml heparin to taurolidine-citrate reduced thrombosis, without an increase in bacteremia, which increased

performance compared to heparin.

In another study, Taylor et al. (21) examined the use of catheter lock taurolidine-citrate in hemodialysis patients in a hospital. They found that the use of taurolidine-citrate, compared to heparin, reduced infections by 85%, as well as the costs and had a positive impact on mortality. Other studies, which were conducted on cancer patients and home parental nutrition, showed that taurolidine-citrate significantly reduced the rate of catheter-related infections (22-24) and resulted in significant savings in costs (25).

Conclusion

The results of this study were consistent with those of previous studies and revealed that taurolidine-citrate has a positive impact on the prevention of catheter-related infections. The result of meta-analysis revealed that the rate of catheter-related infections in hemodialysis patients that have used taurolidine-citrate was 16% less compared to hemodialysis patients who received heparin; and the difference was significant in the incidence of catheter-related thrombosis infections. On the other hand, the rate of catheter-related thrombosis in hemodialysis patients that have used taurolidine-citrate was 13% more compared to hemodialysis patients who received heparin. However, the difference was not significant in the incidence of thrombosis. Considering that taurolidine-citrate has advantages over heparin, more attention should be paid to its benefits in the decision-making process. As mentioned in the results, taurolidine-citrate is an antifungal agent that does not cause bacterial resistance, so if antibiotics are used in combination with heparin, taurolidine-citrate can be more advantageous compared to heparin/antibiotic.

In this search, we could not find any published meta-analysis and cost- effectiveness analysis in electronic databases. The results of the current meta-analysis may be used in different settings to evaluate the efficacy based on available clinical evidences. However, the clinical evidences on taurolidine-citrate, heparin and gentamicin/heparin are not enough for making certain decisions. In addition, the results of cost- effectiveness analysis indicated that in spite of the higher cost of taurolidine-citrate compared to heparin, the total cost is much higher due to the utilization of heparin, and because of the higher rate of catheter-related infection, this new introduced technology can be applied by professionals at the health sector.

In this study, we were faced with some limitations. First, the number of clinical trials evaluating the efficacy and the safety of taurolidine citrate was limited. In addition, the comparator arm in the available RCTs was heparin, and we found only one observational study comparing it to gentamicin. As the clinical efficacy of taurolidine is not compared with other antimicrobial alternatives in available RCTs, the absence of this comparison can be a weakness. The results of the current meta-analysis and cost effectiveness analysis were based on the available clinical evidences on taurolidine- citrate. Therefore, more RCTs comparing the efficacy and safety of taurolidine- citrate with both gentamicin and other antibiotics and anticoagulants, should be piloted and published for more robust results, particularly when these results are used for public health policy making and priority setting.

References

1. Shahbazian H, Ehsanpour A, Ghorbani A, Golzari K, Beladi mousavi S, Hayati F, et al. Epidemiology of Chronic Kidney Disease in Iran and worldwide. Scientific Medical Journal 2010; 9(5):517-27.

2. Beladi Musavi S, Hayati F, Nazari I, Zeraati A. Comparing the use of temporary catheters for dialysis and arteriovenous fistula onset of hemodialysis in patients with end-stage renal disease. Medical Journal of Mashhad University of Medical Sciences 2011;54(2):75-9.

3. Ghane Sherbaf F. Comparison of the complications of central vein catheters and arteriovenous fistulae in children on chronic hemodialysis. Iranian journal of pediatrics 2006;16(4):407-12.

4. AdibHajbagheri M, Molavizadeh N, MasoodiAlavi N. Study of the quality of vascular

access care among hemodialysis patients. International Journal of Critical Care Nursing 2011;4(2):87-92.
5. Fletcher S. Catheter-related bloodstream infection. Continuing Education in Anaesthesia, Critical Care & Pain 2005;5(2):49-51.
6. O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, et al. Guidelines for the prevention of intravascular catheter related infections. Clinical infectious diseases 2002;35(11):1281-307.
7. Goede MR, Coopersmith CM. Catheter-related bloodstream infection. Surgical Clinics of North America 2009;89(2):463-74.
8. Solomon LR, Cheesbrough JS, Ebah L, Al-Sayed T, Heap M, Millband N, et al. A randomized double-blind controlled trial of taurolidine-citrate catheter locks for the prevention of bacteremia in patients treated with hemodialysis. American Journal of Kidney Diseases 2010;55(6):1060.
9. Byrnes MC, Coopersmith CM. Prevention of catheter-related blood stream infection. Current opinion in critical care 2007;13(4):411-5.
10. Filiopoulos V, Hadjiyannakos D, Koutis I, Trompouki S, Micha T, Lazarou D, et al. Approaches to prolong the use of uncuffed hemodialysis catheters: results of a randomized trial. American journal of nephrology 2011;33(3):260-8.
11. Neary PM, Hallihan P, Bouchier-Hayes DJ. The evolving role of taurolidine in cancer therapy. Annals of surgical oncology 2010;17(4):1135-43.
12. Hashemi Meshkini A, Keshavarz K, Gharibnaseri Z, Nikfar S, Abdollahi M. The Effectiveness and Cost-effectiveness of Pregabalin in the Treatment of Diabetic Peripheral Neuropathy: A Systematic Review and Economic Model. International Journal of Pharmacology 2012;8(6): 496-509.
13. Goodman C. HTA 101: Introduction to Health Technology Assessment: National Information Center on Health . USA: Services Research and Health Care Technology; 2004.
14. Keshavarz K, Hashemi-Meshkini A, Zaboli P, Khedmati J. Drug-Eluting Balloon: An Overview of Clinical Evidenc!es on Safety and Effectiveness. Journal of Pharmacoeconomics and Pharmaceutical Management 2001;(1);6-9.
15. Keshavarz K, Hashemi Meshkini A, Gharibnaseri Z, Nikfar S. A systematic cost-effectiveness analysis of pregabalin in the management of fibromyalgia: an Iranian experience. Archives of medical science: AMS 2009 (6); 961-967.
16. Tavanaii-Sani A, Eslami Nokandeh A, Ghorbani H. Evaluation of central venous catheter-related infections in hemodialysis patients. Medical Journal of Mashhad University of Medical Sciences 2012;55(2):110-5.
17. Betjes MG, van Agteren M. Prevention of dialysis catheter-related sepsis with a citrate–taurolidine-containing lock solution. Nephrology Dialysis Transplantation 2004;19(6):1546-51.
18. Eichler HG KS, Gerth WC, Mavros P, Kong SX, Jonsson B. Use of cost effectiveness analysis in health- care resource allocation decision -making: how are cost-effectiveness thresholds expected to emerge? J Value in Health 2004;7(5):518-528.
19. Bradshaw JH, Puntis JW. Taurolidine and catheter-related bloodstream infection: a systematic review of the literature. Journal of pediatric gastroenterology and nutrition 2008;47(2):179-86.
20. Solomon LR, Cheesbrough JS, Bhargava R, Mitsides N, Heap M, Green G, et al. Observational Study of Need for Thrombolytic Therapy and Incidence of Bacteremia using Taurolidine-Citrate-Heparin, Taurolidine-Citrate and Heparin Catheter Locks in Patients Treated with Hemodialysis. Seminars in Dialysis; Wiley Online Library 2012.
21. Taylor C, Cahill J, Gerrish M, Little J. A new haemodialysis catheter-locking agent reduces infections in haemodialysis patients. Journal of renal care 2008;34(3):116-20.
22. Simon A, Ammann RA, Wiszniewsky G, Bode U, Fleischhack G, Besuden MM. Taurolidine-citrate lock solution (TauroLock) significantly reduces CVAD-associated grampositive infections in pediatric cancer patients. BMC infectious diseases 2008;8(1):102.
23. Dumichen M, Seeger K, Lode H, Kühl J, Ebell W, Degenhardt P, et al. Randomized controlled trial of taurolidine citrate versus heparin as catheter lock solution in paediatric patients with haematological malignancies. Journal of Hospital Infection 2012;80(4):304-9.
24. Taniguchi A, Eastwood J, Davidson A, Nightingale J, Gabe S. Effectiveness of Taurolock™ in preventing recurrent catheter-related bloodstream infections in patients on home parenteral nutrition. J Proceedings of the Nutrition Society 2009;68(1):58.
25. Rafferty G, Nightingale J, Small M, Eastwood J, Ugarte Cano C, Intestinal SG. The targeted use of Taurolock® to reduce central venous catheter sepsis in a home parenteral nutrition cohort. J Gut 2010; 59(4):35.

Appendix

Search Strategies

Data Base	Years	Search Strategies	References Identified
PubMed	1996-2013	1)"Taurolock" OR "Taurolidin citrate" 2)"Catheter-related Infection" OR "Catheter-related sepsis" 3)Hemodilysis 4)Heparin lock 5)"1" AND "2" 6)"1" AND "3" 7)"1" AND "4"	231
Scopus			235
Web of knowledge ISI			647
Cochrane			44
Total			1157

What are these studies and their design, aims and results?

Study	Study Design	Aim	Result
Filiopoulos V (2011)	RCT	Compare gentamicin/ heparin and taurolidine/ Citrate and control group (heparin)	Both antimicrobial lock solutions were superior to heparin in CRB prevention with similar thrombosis rates.
Solomon R (2010)	RCT	Comparing taurolidine-citrate catheter locks with heparin catheter locks started at the time of catheter insertion in hemodialysis patients using tunneled cuffed intravascular catheters	Taurolidine-citrate use did not decrease all-cause bacteremia and was associated with a greater need for thrombolytic treatment. There was a decrease in infections caused by Gram-negative organisms and a trend to a lower frequency of bacteremia
Betjes M (2004)	RCT	Tested the efficacy of citrate–taurolidine lock solution compared with heparin in the prevention of Catheter-related sepsis.	Catheter filling with a solution containing the antimicrobial taurolidine may significantly reduce the incidence of catheter related sepsis. Taurolidine appears to be effective and safe and does not carry the risk for side effects that have been reported for other antimicrobial lock solutions containing gentamicin or high concentrations of citrate.
Taylor C (2008)	Observational	Investigating the use of a taurolidine/ citrate catheter-locking agent for patients receiving hospital-based haemodialysis, auditing the number and cost of infections before and after its introduction.	The use of a taurolidine/citrate haemodialysis catheter-locking agent in our haemodialysis population has significantly reduced the line sepsis rate, with a positive impact on morbidity, mortality and cost.
Du¨michen M (2012)	RCT	To compare the impact on microbial catheter colonization and infectious complications of heparin and taurolidine citrate as central venous catheter (CVC) lock solutions in paediatric patients with haematological malignancies.	Use of taurolidine citrate lock solution was associated with significantly fewer primaries BSI.
Simon A (2008)	Cohort	investigated the impact of a taurolidine/citrate containing central venous access device lock solution on catheter-associated infections in a pediatric oncology	The use of Taurolidin/Citrate (TauroLock™) significantly reduced the number and incidence density of primary catheter-associated bloodstream infection in pediatric cancer patients.
Rafferty G (2010)	Cohort	The primary aim was to determine the incidence of CRBSI prior and subsequent to Taurolock® use. The secondary aim was to establish cost benefit from Taurolock® prescription.	Taurolock® significantly decreases CRBSI rate in HPN patients and generates considerable cost savings in this cohort of patients.
Taniguchi A (2009)	Observational	investigated the Effectiveness of TaurolockTM in preventing recurrent catheter-related bloodstream infections in patients on home parenteral nutrition	TaurolockTM proved to be effective in reducing CRBSI significantly in patients with recurrent infections, with acceptable adverse event profile.