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REVIEW

Economic and outcomes consequences of TachoSil®: a systematic review

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Background: TachoSil® is a medicated sponge coated with human fibrinogen and human thrombin. It is indicated as a support treatment in adult surgery to improve hemostasis, promote tissue sealing, and support sutures when standard surgical techniques are insufficient. This review systematically analyses the international scientific literature relating to the use of TachoSil in hemostasis and as a surgical sealant, from the point of view of its economic impact.

Methods: We carried out a systematic review of the PubMed literature up to November 2013. Based on the selection criteria, papers were grouped according to the following outcomes: reduction of time to hemostasis; decrease in length of hospital stay; and decrease in postoperative complications.

Results: Twenty-four scientific papers were screened, 13 (54%) of which were randomized controlled trials and included a total of 2,116 patients, 1,055 of whom were treated with TachoSil. In the clinical studies carried out in patients undergoing hepatic, cardiac, or renal surgery, the time to hemostasis obtained with TachoSil was lower (1–4 minutes) than the time measured with other techniques and hemostatic drugs, with statistically significant differences. Moreover, in 13 of 15 studies, TachoSil showed a statistically significant reduction in postoperative complications in comparison with the standard surgical procedure. The range of the observed decrease in the length of hospital stay for TachoSil patients was 2.01–3.58 days versus standard techniques, with a statistically significant difference in favor of TachoSil in eight of 15 studies.

Conclusion: This analysis shows that TachoSil has a role as a supportive treatment in surgery to improve hemostasis and promote tissue sealing when standard techniques are insufficient, with a consequent decrease in postoperative complications and hospital costs.

Keywords: TachoSil®, systematic review, economic evaluation, cost analysis, outcomes research

Introduction

Hemorrhage is a normal physiologic response to a tissue lesion involving the vascular system, and can be caused by a topical or systemic medical or surgical intervention.[1] The process of hemostasis is triggered when there is a leakage from the vascular bed and is followed by the process of coagulation, whereby a number of factors lead to formation of a clot which subsequently undergoes lysis via fibrinolysis.[2,3] During bleeding, mechanical hemostasis can be achieved using traditional methods, such as manual pressure or tourniquets, compressive bandages, ligatures, sutures, clippings, or electrocautery by means of monopolar or bipolar electroscalpels.[4]

Newer systems for vascular synthesis and coagulation, however, use a combination of pressure (through the handpiece-forceps) and radiofrequency applied to the

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target tissues.[5] Thus, hemostasis does not depend on thrombus formation in the proximal vessel, but is the result of fusion of collagen and elastin in the intimal part of the vessel, which creates permanent scarring.[6] Broadly, these systems are divided in three categories, ie, hemostatic dressings, surgical sealants, and blood-derived local hemostatic agents.

Hemostatic dressings are medical devices that can be derived from plants (polysaccharides, cellulose-derived products), animals (collagen and gelatin), or minerals (zeolite, only removable surgically). Their mechanism of action is chemical and/or mechanical, and they promote platelet aggregation on the surface of the wound/cut, creating a substrate for the coagulation cascade. Surgical sealants are also medical devices and can be of synthetic or semisynthetic origin. In the presence of water, the sealant is polymerized and interacts with the coagulation cascade by an exclusively mechanical action.[3] The introduction of local hemostatic products identified as topical drugs of human or animal origin is more recent.[7,8] These products (eg, Artiss® [Baxter International Inc., Deerfield, IL, USA], Beriplast® [CSL Behring, King of Prussia, PA, USA], Evicel® [OMRIX Biopharmaceuticals Ltd, Nes-Ziona, Israel], Quixil® [OMRIX Biopharmaceuticals Ltd] TachoSil® [Takeda Austria GmbH, Linz, Austria], and Tisseel® [Baxter International Inc.]) have two mechanisms of action, ie, they either work on the coagulation cascade with a metabolic hemostatic action or have a mechanical action as adhesive hemostatic agents.

These different product categories sometimes have the same clinical indications, ie, some facilitate hemostasis while others facilitate hemostasis, promote sealing, and support sutures.[3] TachoSil, for example, is an equine-derived collagen sponge coated on one side with human fibrinogen and human thrombin. It is indicated as supportive treatment in adults undergoing surgery to improve hemostasis, promote tissue sealing, and support suturing in vascular surgery where standard techniques are inadequate.[7,8] Unlike other drugs, TachoSil does not have special storage requirements (temperature below 25°C) and is ready for use.

The studies reported in the literature regarding the efficacy of these new products are often flawed by methodological errors and not rigorously conducted.[9] In general, the studies available are not controlled and have been carried out in a limited number of surgical areas, so although these products are very widely used in a number of scenarios in clinical practice, their use is generally off-label. Research and evaluation of their potential economic impact on health care systems is even more limited, which makes it difficult for decision-makers (ie, physicians and pharmacists) to make cost-effective choices in a contest of increasing sustainability of expenditure.

Materials and methods

The aim of this review was to analyze the international scientific literature relating to the use of TachoSil in hemostasis and as a surgical sealant, from the point of view of its economic impact. We therefore carried out a systematic review of the PubMed literature up to November 2013,[10] and reviewed economic evaluations comparing one or more alternatives in terms of costs and/or consequences for health care systems.[9,11] The scientific papers were screened and selected based on the following inclusion criteria: clinical and economic evaluation of cost of treatment alone, cost-effectiveness, cost-utility, cost-benefit, and publication in English. Abstracts and posters were felt to lack sufficient information and therefore were not considered for inclusion. The key search terms used were "TachoSil" and "cost(s)", "economic(s)", "pharmacoeconomics", "outcome research", "topical hemostatic agents", "fibrinogen", "thrombin", "hemostatic agents", "randomized clinical trial", and "surgical hemostasis". Papers were selected if they contained clinical data showing a clear impact on use of resources by health care system (National Health Service [NHS], health care funds or insurance), if TachoSil was compared with other options (ie, standard suturing techniques, medical devices, surgical sealants, other hemostatic products) to improve postoperative hemostasis, and if the consequences for length of hospital stay and postoperative complications were reported.

Results

The results of this systematic analysis are shown in Figure 1. Of 358 potential papers identified, 334 were excluded because they were not economic evaluations (n=143), included comparisons of drugs other than those considered in this review (n=115), or were published as case reports (n=8).

Twenty-four scientific papers were identified for inclusion in the study, 13 of which (54%) were randomized controlled trials and nine (37%) were prospective cohort studies. The studies identified included a total of 2,116 patients, 1,055 of whom were treated with TachoSil. According to our selection criteria, the papers were grouped according to the following outcomes: decrease in time to hemostasis, reduction in length of hospital stay, and decrease in postoperative complications.[10]

Impact on time to hemostasis

Six of the selected papers were randomized controlled trials in patients undergoing hepatic, cardiac, or renal surgery.[12–17]

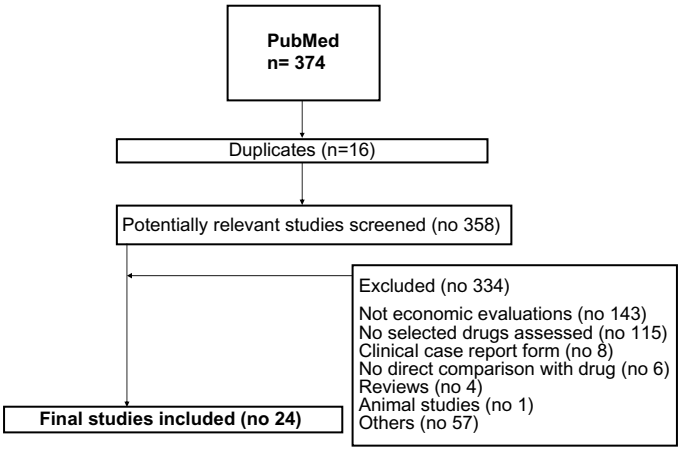

Figure 1 Flow diagram of the selection process to identify studies to be included.

Time to hemostasis with TachoSil was less (1–4 minutes) than that using other techniques. In patients undergoing cardiac surgery, hemostasis was reached in 3 minutes in 75% of cases using TachoSil versus 33% with other techniques.[14,15] In total, 609 patients were included, 295 of whom were treated with TachoSil. The differences in time to hemostasis were statistically significant in five of the six papers[13–17] (Table 1).

Change in length of hospital stay

Length of hospital stay was reported by 15 of the selected papers (62% of the total number of studies screened), which were carried out in patients undergoing pulmonary, hepatic, kidney, cardiac, or gastric surgery. Seven studies (46%) were randomized controlled trials[18–24] and eight were prospective cohort studies.[25–32] These studies included 1,426 patients, 723 of whom were treated with TachoSil (Table 2). A decrease in the length of postoperative hospital stay (by 2.01–3.58 days) was found for patients treated with TachoSil when compared with those treated using standard techniques. It is interesting to note that the decrease in length of hospital stay was greater in TachoSil-treated patients undergoing gastric or hepatic surgery, who showed a mean reduction in hospital stay of 3.58 and 2.33 days, respectively. Eight (53%) of the 15 studies showed a statistically significant difference in favour of TachoSil. Further, two randomized controlled trials showed that use of TachoSil in pulmonary surgery generated savings in the range of 98.00–205.50 Euros per patient when compared with standard techniques.[22,23]

Table 1 Time to hemostasis reduction: TachoSil versus other standard techniques

Author	Year	Countries	Design	Surgery	Sealing agents	Patient no	Time to hemostasis	Statistical difference (*P*-value)
Kakaei et al[12]	2013	Iran	Randomized clinical trial	Hepatic	TachoSil	15	3.0 min	*P*=0.43
					Surgicel	15	3.2 min	
					Glubran 2	15	2.6 min	
Fischer et al[13]	2011	Germany, Austria, Denmark	Randomized clinical trial	Hepatic	TachoSil	60	3.6 min	*P*=0.001
					Argon coagulator	59	5.0 min	
Bajardi et al[14]	2009	Italy	Randomized clinical trial	Cardiac	TachoSil	10	264±127.1 sec	*P*=0.02
					Standard technique	10	408±159.5 sec	
Maisano et al[15]	2009	Germany, Denmark, Spain, France, Italy	Randomized clinical trial	Cardiac	TachoSil	59	After 3.6 min: 75%	*P*<0.0001
					Standard technique	60	After 3 min: 33%	
Siemer et al[16]	2007	Germany, Austria, Belgium	Randomized clinical trial	Renal	TachoSil	92	5.3 min	*P*<0.0001
					Standard technique	93	9.5 min	
Frilling et al[17]	2005	Germany	Randomized clinical trial	Hepatic	TachoSil	59	3.9 min	*P*=0.0007
					Argon coagulator	62	6.3 min	

Abbreviations: min, minutes; sec, seconds.

Table 2 Hospital stay length reduction: TachoSil versus standard technique

Author	Year	Countries	Design	Surgery	Sealing agents	Patient no	Hospital stay (days)	Statistical difference (*P*-value)
Filosso et al[18]	2013	Italy	Randomized clinical trial	Lung	TachoSil	13	6.9	$P<0.001$
					Standard technique	11	9.5	
Cormio et al[24]	2012	Italy	Randomized clinical trial	Kidney	TachoSil	50	2.75 (±1.78)	$P<0.0001$
					Standard technique	50	5.15 (±1.74)	
Montorsi et al[19]	2012	Italy	Randomized clinical trial	Pancreatic	TachoSil	145	7	ns
					Standard technique	130	10	
Pilone et al[20]	2012	Italy	Randomized clinical trial	Gastric	TachoSil	15	6.5	ns
					Standard technique	15	7	
De Rosa et al[25]	2011	Italy	Prospective cohort	Hepatic	TachoSil	15	6.7	ns
					Standard technique	10	8.3	
Pavlik et al[26]	2011	Norway	Retrospective cohort	Pancreatic resection	TachoSil	73	5 (2–16)	ns
					Standard technique	48	5.5 (2–35)	
De Stefano et al[27]	2011	Italy	Prospective cohort	Gastric	TachoSil	24	7.2	ns
					Standard technique	39	9.3	
Briceno et al[28]	2010	Spain	Prospective cohort	Hepatic	TachoSil	57	9.6±5.1	$P=0.03$
					Standard technique	58	12.6±6.7	
Marta et al[21]	2010	Germany, Austria, Denamark, Hungary, Italy	Randomized clinical trial	Lung	TachoSil	148	8 (1–36)	$P=0.35$
					Standard technique	151	9 (4–28)	
Padillo et al[29]	2010	Spain	Prospective cohort	Pancreatic transplant	TachoSil	34	22.8±11.1	$P=0.03$
					Standard technique	34	34.6±11.3	
Rena et al[30]	2009	Italy	Prospective cohort	Lung	TachoSil	30	5.87±1.07	$P=0.01$
					Standard technique	30	7.50±3.20	
Anegg et al[22]	2008	Germany, Austria	Randomized clinical trial	Lung	TachoSil	75	6.20	$P=0.01$
					Standard technique	77	7.7	
Droghetti et al[23]	2008	Italy	Randomized clinical trial	Lung	TachoSil	20	11.00 (9–17)	$P=0.73$
					Standard technique	20	14.3 (8–57)	
Onorati et al[31]	2008	Italy	Prospective cohort	Cardiac	TachoSil	11	6.2±0.4	$P=0.01$
					Standard technique	18	8.9±3.3	
Barranger et al[32]	2007	France	Prospective cohort	Breast	TachoSil	13	3.5	ns
					Standard technique	12	5.5	

Abbreviation: ns, no statistically significant difference.

Decrease in postoperative complications

Reduction in postoperative complications was assessed in 15 studies carried out in patients undergoing pulmonary, hepatic, kidney, cardiac, or gastric surgery. Eight studies (53%) were randomized controlled trials[12,18,19,21–24,33] and six were prospective cohort studies.[28–31,34,35] These studies included 1,470 patients, 738 of whom were treated with TachoSil (Table 3). Postoperative complications included air leaks (for lung surgery), intra-abdominal infections, asymptomatic lymphocele, pericardial complications, postoperative fistulas, and others.

Air leaks are common after pulmonary surgery, and can result in serious complications, such as empyema and a protracted hospital stay.[36] Air leaks were reported to occur in up to 58% of lobectomy procedures, depending on the surgical technique used.[37] Our review identified a 9%–45% decrease in air leaks in five studies (four of which were randomized) using TachoSil when compared with standard techniques.[18,21–23,30]

The literature screened showed that TachoSil plays a role in decreasing intraoperative complications and postoperative air leaks, in addition to other postoperative complications (Table 3). It is important to keep in mind that a decrease in complications translates into a reduction in length of hospital stay (Table 2). In 13 of the 15 papers we identified, TachoSil achieved a statistically significant reduction in the number of postoperative complications when compared with standard techniques.

Discussion

In the current health care scenario of increasing costs, evaluation of the potential benefits of any given treatment should

Table 3 Reduction in postoperative complications: TachoSil versus other standard techniques

Author	Year	Countries	Design	Surgery	Sealing agents	Patient no	Postoperative complications	Statistical difference (*P*-value)
Air leaks (lung surgery)								
Filosso et al[18]	2013	Italy	Randomized clinical trial	Lung	TachoSil	13	4.7/days air leaks	$P<0.001$
					Standard technique	11	10/days	
Marta et al[21]	2010	Germany, Austria, Denmark, Hungary, Italy	Randomized clinical trial	Lung	TachoSil	148	Global: 32%	$P=0.022$
					Standard technique	151	Global: 58%	
Rena et al[30]	2009	Italy	Prospective cohort		TachoSil	30	Global: 55%	$P=0.03$
					Standard technique	30	Global: 96%	
Anegg et al[22]	2008	Austria, Germany	Randomized clinical trial	Lung	TachoSil	75	Day 1: 43.6 mL/minutes	$P=0.004$
					Standard technique	77	Day 1: 86.1mL/minutes	
Droghetti et al[23]	2008	Italy	Randomized clinical trial	Lung	TachoSil	20	Global: 50%	$P=0.001$
					Standard technique	20	Global: 95%	
Intra-abdominal infections								
Padillo et al[29]	2010	Spain	Prospective cohort	Pancreatic transplant	TachoSil	34	0%	$P=0.003$
					Standard technique	34	32%	
Development of asymptomatic lymphocele								
Simonato et al[33]	2009	Italy	Randomized clinical trial	Prostate	TachoSil	30	5%	$P=0.001$
					Standard technique	30	19%	
Pericardial complications								
Onorati et al[31]	2008	Italy	Prospective cohort	Cardiac	TachoSil	11	0%	$P=0.039$
					Standard technique	18	33%	
Postoperative fistulas								
Montorsi et al[19]	2012	Italy	Randomized clinical trial	Pancreatic	TachoSil	145	62.00%	$P=0.267$
					Standard technique	130	68.00%	
Pavlik et al[26]	2011	Norway	Retrospective cohort	Pancreatic resection	TachoSil	73	8.00%	$P=0.487$
					Standard technique	48	12.00%	
Other complications								
Kakaei et al[12]	2013	Iran	Randomized clinical trial	Hepatic	TachoSil	15	Postoperative bleeding: 0	$P=0.04$
					Surgicel	15	Postoperative bleeding: 33%	
					Glubran 2	15	Postoperative bleeding: 13.3%	
Cormio et al[24]	2012	Italy	Randomized clinical trial	Kidney	TachoSil	50	Tract complication: 2%	$P<0.001$
					Standard technique	50	Tract complication: 25.5%	
Buda et al[34]	2012	Italy	Case-controlled analysis	Vulvar/ovarian and breast cancer	TachoSil	8	Lower drainage volume: 133 mL	$P<0.001$
					Standard technique	16	Lower drainage volume: 320 mL	
Briceno et al[28]	2010	Spain	Prospective cohort	Hepatic	TachoSil	57	Postoperative complications: 8%	$P=0.03$
					Standard technique	58	Postoperative complications: 21%	
Tamasauskas et al[35]	2008	Lithuania	Prospective cohort	Neurosurgery	TachoSil	29	Postoperative cerebrospinal fluid leak: 13.8%	$P=0.02$
					Standard technique	29	Postoperative cerebrospinal fluid leak: 41.4%	

take into account its cost-effectiveness in comparison with standard treatments as well as its medium-term and long-term effects on both clinical outcome and total health care costs.[38] Systematic literature reviews identify, assess, and summarize the results of individual studies, and make these results available and more accessible to health care decision-makers.[9] This review of the literature shows the relevance of TachoSil as a supportive treatment in surgery to improve hemostasis and promote tissue sealing when standard techniques are inadequate. Our findings are strengthened by the high number of studies screened (n=24), 54% of which were randomized controlled trials and included a total of 2,116 patients. A statistically significant difference in favor of TachoSil was found in eight of 15 (53%) screened studies for decreased length of hospital stay and in 13 of 15 (87%) for reduction in postoperative complications, with a consequent decrease in hospital expenditure. Similar results were reported in a previous systematic review of the literature addressing the economic impact of TachoSil,[10] but the number of papers we reviewed (n=24) was much higher than that identified in the earlier review in 2011 (n=15). Our review highlights further the role of TachoSil in reducing hospital costs and postoperative complications in a larger number of patients.

Moreover, as confirmed by other systematic reviews, TachoSil also helps to decrease the number of blood transfusions required.[7] From an economic point of view, the 4-minute decrease in time to hemostasis observed for TachoSil with respect to standard techniques translates into reduced theater time and less staff requirements per treated patient. Finally, TachoSil is very easy to store (room temperature, 3-year shelf-life) and use (no requirement for thawing). This makes it a reference product for comparison with other hemostatic drugs, such as Tisseel, Quixil, Evicel, or Artiss.[3]

This review has some limitations. Not all the selected studies were randomized controlled trials (54%) and the economic endpoint was generally secondary in the design of these studies. Moreover, no pharmacoeconomic simulation models were included. Such pharmacoeconomic studies would have helped decision-makers by highlighting the key elements for choice of the best topical hemostatic agent and surgical sealant and would also help clinicians in outlining prospective economic evaluations and in correctly quantifying the costs of treatment.[39]

Some health economists have criticized the value of systematic reviews for economic evaluations in the health care setting.[40] When conducting a systematic search, it is possible that not all relevant studies are identified. On the other hand, as discussed by other researchers,[38,40] search terms like "economic evaluation", "economics", and "cost" in studies can lead to identification of a number of studies which are potentially irrelevant to a systematic review.

Moreover, differences in study design and methodology make it extremely difficult to synthetize the studies identified in a coherent set. However, methods have now been developed to guide such reviews,[9,41] and a large number of systematic reviews have been conducted in various therapeutic areas, including ischemic stroke,[42] chronic obstructive pulmonary disease,[43] and hepatitis B and C.[44,45] In the future, our ability to identify which topical hemostatic agent or surgical sealant should be used in a particular patient will depend increasingly on the quality of information available regarding prevention of postoperative complications in clinical practice and, indirectly, on the possibility of optimizing the use of hospital services. High-quality information would be necessary to optimize total health expenditure and simultaneously improve patient quality of life.

Disclosure

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References

1. Harmon DE. Cost/benefit analysis of pharmacologic hemostasis. *Ann Thorac Surg*. 1996;61(Suppl 2):S21–S25.
2. Hartmann M, Sucker C, Boehm O, Koch A, Loer S, Zacharowski K. Effects of cardiac surgery on hemostasis. *Transfus Med Rev*. 2006;20:230–241.
3. Regione Emilia Romagna, Commissione Regionale Dispositivi Medici (Delibera Giunta Regionale n. 1523/2008). Emostatici locali e sigillanti chirurgici Dalle evidenze della letteratura alla pratica quotidiana, Novembre 2012. Available from: http://www.saluter.it/documentazione/rapporti/emostatici_novembre2012.pdf. Accessed November 28, 2013. Italian.
4. Vonlanthen R, Slankamenac K, Breitenstein S, et al. The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. *Ann Surg*. 2011;254:907–913.
5. Sundaram CP, Keenan AC. Evolution of hemostatic agents in surgical practice. *Indian J Urol*. 2010;26:374–378.
6. Spotnitz WD. Hemostats, sealants, and adesive: a practical guide for the surgeon. *Am Surg*. 2012;78:1305–1321.
7. Rickenbacher A, Breitenstein S, Lesurtel M, Frilling A. Efficacy of TachoSil – a fibrin-based hemostat in different fields of surgery. A systematic review. *Expert Opin Biol Ther*. 2009;9:897–907.
8. Spotnitz WD, Burks S. Hemostats, sealants, and adhesive III: a new update as well as cost and regulatory considerations for components of the surgical toolbox. *Transfusion*. 2012;52:2243–2255.
9. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. University of York, 2008. Available from: http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf. Accessed October 30, 2013.

10. Rubio-Terrés C, Rubio-Rodríguez D. Efficiency of TachoSil® in hemostasis and surgical sealing. *PharmacoEconomics – Spanish Research Articles*. 2011;8:96–105.
11. Drummond MF, Sculpher MJ, Torrance GW, et al. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd ed. New York, NY, USA: Oxford University Press; 2005.
12. Kakaei F, Seyyed Sadeghi MS, Sanei B, Hashemzadeh S, Habibzadeh A. A randomized clinical trial comparing the effect of different hemostatic agents for hemostasis of the liver after hepatic resection. *HPB Surg*. 2013;2013:587608.
13. Fischer L, Seiler CM, Broelsch CE, de Hemptinne B, Klempnauer J, Mischinger HJ. Hemostatic efficacy of TachoSil in liver resection compared with argon beam coagulator treatment: an open, randomized, prospective, multicenter, parallel-group trial. *Surgery*. 2011;149:48–55.
14. Bajardi G, Pecoraro F, Mirabella D. Efficacy of TachoSil® patches in controlling Dacron suture-hole bleeding after abdominal aortic aneurysm open repair. *J Cardiothoracic Surg*. 2009;4:60.
15. Maisano F, Kjærga HK, Bauernschmitt R, Pavie A, Rábago G, Laskar M. TachoSil surgical patch versus conventional hemostatic fleece material for control of bleeding in cardiovascular surgery: a randomised controlled trial. *Eur J Cardiothoracic Surg*. 2009;36:708–714.
16. Siemer S, Lahme S, Altziebler S, Machtens, et al. Efficacy and safety of TachoSil as hemostatic treatment versus standard suturing in kidney tumour resection: a randomised prospective study. *Eur Urol*. 2007;52:1156–1163.
17. Frilling A, Stavrou GA, Mischinger HJ, et al. Effectiveness of a new carrier-bound fibrin sealant versus argon beamer as hemostatic agent during liver resection: a randomised prospective trial. *Langenbecks Arch Surg*. 2005;390:114–120.
18. Filosso PL, Ruffini E, Sandri A, Lausi PO, Giobbe R, Oliaro A. Efficacy and safety of human fibrinogen-thrombin patch (TachoSil®) in the treatment of postoperative air leakage in patients submitted to redo surgery for lung malignancies: a randomized trial. *Interact Cardiovasc Thorac Surg*. 2013;16:661–666.
19. Montorsi M, Zerbi A, Bassi C, Capussotti L, Coppola R, Sacchi M; Italian Tachosil Study Group. Efficacy of an absorbable fibrin sealant patch (TachoSil) after distal pancreatectomy: a multicenter, randomized, controlled trial. *Ann Surg*. 2012;256:853–859.
20. Pilone V, Di Micco R, Monda A, Villamaina E, Forestieri P. Use of Tachosil® in bariatric surgery: preliminary experience in control of bleeding after sleeve gastrectomy. *Minerva Chir*. 2012;67:241–248.
21. Marta GM, Facciolo F, Ladegaard L, et al. Efficacy and safety of TachoSil versus standard treatment of air leakage after pulmonary lobectomy. *Eur J Cardiothorac Surg*. 2010;38:683–689.
22. Anegg U, Rychlik R, Smolle-Jüttner F. Do the benefits of shorter hospital stay associated with the use of fleece-bound sealing outweigh the cost of the materials? *Interact Cardiovasc Thorac Surg*. 2008;7:292–296.
23. Droghetti A, Schiavini A, Muriana P, et al. A prospective randomized trial comparing completion technique of fissures for lobectomy: stapler versus precision dissection and sealant. *J Thorac Cardiovasc Surg*. 2008;136:383–391.
24. Cormio L, Perrone A, Di Fino G, et al. TachoSil(®) sealed tubeless percutaneous nephrolithotomy to reduce urine leakage and bleeding: outcome of a randomized controlled study. *J Urol*. 2012;188:145–150.
25. De Rosa P, Valeriani G, Barbato G, et al. Postexplant residual cavity hemostasis with a TachoSil patch. *Transplant Proc*. 2011;43:1069–1071.
26. Pavlik Marangos I, Røsok BI, Kazaryan AM, Rosseland AR, Edwin B. Effect of TachoSil patch in prevention of postoperative pancreatic fistula. *J Gastrointest Surg*. 2011;15:1625–1629.
27. De Stefano A, Bettarini F, Di Mare G, Neri A. [Enteric anastomosis and Tachosil®]. *Minerva Chir*. 2011;66:183–188. Italian.
28. Briceño J, Naranjo A, Ciria R, et al. A prospective study of the efficacy of clinical application of a new carrier-bound fibrin sealant after liver resection. *Arch Surg*. 2010;145:482–488.
29. Padillo J, Arjona-Sánchez A, Ruiz-Rabelo J, Regueiro JC, Canis M, Rodríguez-Benot A. Human fibrinogen patches application reduces intra-abdominal infectious complications in pancreas transplant with enteric drainage. *World J Surg*. 2010;34:2991–2996.
30. Rena O, Papalia E, Mineo TC, et al. Air-leak management after upper lobectomy in patients with fused fissure and chronic obstructive pulmonary disease: a pilot trial comparing sealant and standard treatment. *Interact Cardiovasc Thorac Surg*. 2009;9:973–977.
31. Onorati F, Pasceri E, Scalas C, et al. Aortic tube grafts wrapping with hemostatic fleeces reduces postoperative pericardial effusions. *J Cardiovasc Surg (Torino)*. 2008;49:1–5.
32. Barranger E, Morel O, Akerman G, Malartic C, Clement D. Tachosil® to reduce the morbidity of axillary lymph node dissection in breast cancer. *Breast Cancer Res*. 2007;9 Suppl 1:P21.
33. Simonato A, Varca V, Esposito M, Venzano F, Carmignani G. The use of a surgical patch in the prevention of lymphoceles after extraperitoneal pelvic lymphadenectomy for prostate cancer: a randomized prospective pilot study. *J Urol*. 2009;182:2285–2290.
34. Buda A, Fruscio R, Pirovano C, Signorelli M, Betti M, Milani R. The use of TachoSil for the prevention of postoperative complications after groin dissection in cases of gynecologic malignancy. *Int J Gynaecol Obstet*. 2012;117(3):217–219.
35. Tamasauskas A, Sinkunas K, Draf W, et al. Management of cerebrospinal fluid leak after surgical removal of pituitary adenomas. *Medicina (Kaunas)*. 2008;44:302–307.
36. Belda-Sanchís J, Serra-Mitjans M, Iglesias Sentis M, Rami R. Surgical sealant for preventing air leaks after pulmonary resections in patients with lung cancer. *Cochrane Database Syst Rev*. 2010;1:CD003051.
37. Okereke I, Murthy SC, Alster JM, Blackstone EH, Rice TW. Characterization and importance of air leak after lobectomy. *Ann Thorac Surg*. 2005;79:1167–1173.
38. Simoens S. How to assess the value of medicines? *Front Pharmacol*. 2010;1:115.
39. Colombo GL, Di Matteo S, Maggiolo F. Antiretroviral therapy in HIV-infected patients: a proposal to assess the economic value of the single-tablet regimen. *Clinicoecon Outcomes Res*. 2013;5:59–68.
40. Anderson R. Systematic reviews of economic evaluations: utility or futility? *Health Econ*. 2010;19:350–364.
41. Carande-Kulis VG, Maciosek MV, Briss PA, et al. Methods for systematic reviews of economic evaluations for the Guide to Community Preventive Services. Task Force on Community Preventive Services. *Am J Prev Med*. 2000;18(Suppl 1):75–91.
42. Jung KT, Shin DW, Lee KJ, et al. Cost-effectiveness of recombinant tissue plasminogen activator in the management of acute ischemic stroke: a systematic review. *J Clin Neurol*. 2010;6:117–126.
43. Mauskopf JA, Baker CL, Monz BU, et al. Cost effectiveness of tiotropium for chronic obstructive pulmonary disease: a systematic review of the evidence. *J Med Econ*. 2010;13:403–417.
44. Sroczynski G, Esteban E, Conrads-Frank A, et al. Long-term effectiveness and cost-effectiveness of antiviral treatment in hepatitis C. *J Viral Hepat*. 2010;17:34–50.
45. Buti M, Oyagüez I, Lozano V, Casado MA. Cost effectiveness of first-line oral antiviral therapies for chronic hepatitis B: a systematic review. *Pharmacoeconomics*. 2013;31:63–75.