Kidney Cancer

Efficacy and Safety of TachoSil® as Haemostatic Treatment versus Standard Suturing in Kidney Tumour Resection: A Randomised Prospective Study

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Abstract

Objectives: Elective nephron-sparing surgery (NSS) for renal cell carcinoma (RCC) has gained general acceptance as an alternative to radical nephrectomy. To achieve haemostasis without risk of local ischaemia and necrosis of kidney parenchyma after standard haemostatic suturing, we investigated TachoSil’s® efficacy and safety as atraumatic haemostatic treatment after kidney tumour resection.

Methods: A total of 185 patients scheduled for NSS for small, superficial kidney tumours were included in an open, randomised, prospective, multicentre, parallel-group trial. Primary objectives were to test haemostatic efficacy and safety of TachoSil versus standard suturing. Efficacy was tested by comparing intraoperative time to haemostasis (primary end point). Secondary objectives included proportion of subjects with haemostasis after 10 min of trial treatment, occurrence of haematoma on day 2 after surgery, volume and haemoglobin concentration of postoperative drainage fluid, and surgeon’s rating of usefulness of trial treatments. Safety was evaluated by occurrence of adverse events.

Results: In the intent-to-treat population, time to haemostasis was significantly shorter with TachoSil versus standard suturing (mean: 5.3 vs. 9.5 min [p < 0.0001]). Haemostasis was obtained within 10 min in 92% of patients in the TachoSil group and in 67% in the standard treatment group (p < 0.0001). Differences in other secondary end points were not statistically significant. Both treatments were well tolerated. Surgeons rated TachoSil higher in terms of convenience to prepare and apply, and impression of efficacy.

Conclusion: TachoSil was superior to standard suturing in obtaining intraoperative control of haemorrhage and was as well tolerated as standard haemostatic treatment during NSS.

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1. Introduction

Over recent years, nephron-sparing surgery (NSS) has become the standard treatment for small (<4 cm), peripherally located kidney tumours in patients with a normal contralateral kidney [1–4]. The benefits of NSS include decreased risk of renal insufficiency [5] and positive impact on quality of life [6,7]. It is likely that partial nephrectomy will become increasingly common [8]. In addition, recent publications recommend nephron-sparing surgery even in selected patients with localised RCC >4 cm with an optimal long-term outcome [9–12].

However, despite the move towards less extensive surgery and the availability of numerous treatment modalities, intra- and postoperative haemorrhage of the kidney resection surface remains a challenge. The current standard haemostatic method is suturing, although actual techniques may vary slightly between centres.

TachoSil is a sterile ready-to-use absorbable patch for intraoperative topical application. It consists of an equine collagen patch coated with the fibrin glue components, human fibrinogen and human thrombin. It thus combines the assets of a pliable patch material with the haemostatic and adhesive properties of the coagulation factors. The product is currently approved in Europe for supportive haemostatic treatment in surgery. The efficacy and safety of Tachosil have been demonstrated in liver resection [12,14] and pulmonary lobectomy [15,16] trials. The predecessors of TachoSil (TachoComb® and TachoComb® H) have proven to be efficacious haemostats and tissue sealants from several years of clinical use.

This study evaluated TachoSil as a haemostatic adjunct treatment in NSS and compared the haemostatic efficacy and safety of TachoSil with standard suturing.

2. Materials and methods

2.1. Study design and objectives

This was an open, randomised, prospective, multicentre and multinational, parallel group phase 3 trial. Resection of small, superficial kidney tumours not extending into the collecting duct system were performed by open surgery by using standard techniques. However, use of laser scalpel, infrared coagulator, or argon beamer was not allowed for the resection, and the integrity of the pelvicalyceal system was to be maintained. Primary control of major haemorrhagic points was performed by using sutures and ligations until pulsating arterial and/or major venous bleeding was absent. Patients were then eligible for randomisation to TachoSil or standard suturing for the treatment of residual haemorrhage. No other secondary treatment was allowed during the 10-min assessment period, after which any hemostatic treatment could be applied except TachoSil. Block randomisation was according to a pregenerated random number list, and allocation concealment until start of secondary haemostatic treatment was ensured by the sealed code envelope method to avoid selection bias. The size of the TachoSil patch was 9.5 × 4.8 × 0.5 cm, and as many patches as needed were used to cover haemorrhagic sites at least 1 cm beyond immediate margins.

The primary end point was intraoperative time to haemostasis (minutes) in the intent-to-treat (ITT) population. The study was powered for the primary end point only, that is, the predefined sample size was estimated only for this outcome variable. Haemostasis was achieved when there was no visible bleeding from the target site. Presence or absence of haemostasis was assessed by the surgeon and recorded at 3, 4, and 5 min after the first application was started. In case haemostasis was not obtained at 5 min, trial treatment was to be repeated. Assessment of haemostasis was repeated at 8, 9, and 10 min. If haemostasis was not obtained at 10 min, the actual time to haemostasis (more than 10 min) was recorded. Assessments were performed by the surgeon inspecting the target site for bleeding. The assessments were not blinded because of the appearance of treatments. Temporary occlusion of renal blood flow by clamping was optional but should be released during assessment of haemorrhage. Standardisation of the assessment regimen for time to haemostasis was ensured by a detailed definition in the trial protocol and thorough training of the surgeons at trial initiation.

Secondary end points included the occurrence of haemotoma detected by ultrasonography on day 2 after surgery and the proportion of subjects with haemostasis after 10 min of trial treatment. The ultrasonographic assessment was standardised by a predefined 4-point classification, which consisted of no sign, minimal sign, clearly defined and <5 cm in diameter, and clearly defined and >5 cm in diameter. Further exploratory efficacy assessments included description of volume and haemoglobin concentration of postoperative drainage fluid and surgeon’s rating of usefulness of trial treatments, which were recorded on a scale from 1 (bad) to 5 (good) and included convenience of preparation, convenience of application, and impression of intraoperative haemostatic efficacy.

Safety was evaluated by occurrence of adverse events according to good clinical practice.

2.2. Patients

A sample size of 170 patients was precalculation-based on a statistical power of 90%, a significance level of 5%, and an
expected time to haemostasis of 4.5 ± 0.5 and 8.0 ± 0.5 min for TachoSil and standard treatment, respectively. Patients aged ≥18 yr and scheduled for resection of small, superficial kidney tumours (not infiltrating the urinary tract and not requiring major kidney resection or extirpation) were eligible for inclusion in the study. Study exclusions included patients undergoing emergency operations; those with evidence of coagulation disorders, abnormal prothrombin time, or activated partial thromboplastin time; those who were pregnant or breast-feeding.

Preoperative screening took place within 7 d of planned surgery and included full assessment of inclusion/exclusion criteria, physical examination, and full medical history. Further assessments took place on the day of surgery, on day 1 and day 2 after surgery, and on discharge from the surgical ward. A follow-up assessment took place 1 mo after surgery and was carried out in the hospital or over the telephone.

The study was conducted according to the Declaration of Helsinki and good clinical practice, and was approved by independent ethics committees with all patients giving informed consent.

2.3. Statistical analysis

Time to haemostasis was analysed for the ITT population using a life-table analysis and a log-rank test of equality over treatment. The proportion of subjects with haemostasis after 10 min was compared between treatments with the Cochran-Mantel-Haenszel test controlling for centre. The difference between treatments in haematoma formation 2 d after surgery was assessed with the Mann-Whitney U test. Changes in laboratory values from screening were compared between treatments with the Mann-Whitney U test. Data are presented by descriptive statistics: n, mean (median, range), and SD. The differences between treatments of the most frequent adverse events were tested by a two-sided Fisher exact test.

3. Results

A total of 208 patients were screened, with 185 being included in the trial at 13 centres in Austria, Belgium, and Germany between September 2002 and October 2004. The ITT population consisted of patients randomly allocated to TachoSil (n = 92) and standard suturing (n = 93). A total of 3 patients discontinued from the trial (TachoSil: 1 patient because of nephrectomy and 1 because of patient noncompliance; standard suturing: 1 patient because of nephrectomy; Fig. 1). One TachoSil patch was used in 71 subjects (77%), two patches in 18 (20%), and three in 3 subjects (3%).

3.1. Baseline data

Baseline characteristics of the two groups were well matched, although patients treated with TachoSil were more likely to smoke and were 3 yr younger (Table 1). All patients were Caucasian, with a mean age of 63 yr and mean body mass index (BMI) of 27.6 kg/m².

3.2. Surgery

The mean area of the resection wound was similar in both groups, being 8.2 cm² and 8.1 cm² for TachoSil and suturing, respectively. Likewise, there were no differences between treatment groups in cutting techniques, and methods and time used for primary control of haemorrhage. Temporary renal clamping was done in 52% and 62% of the TachoSil and standard groups, respectively (Table 2).

3.3. Primary efficacy end point

Mean (median) time to haemostasis in the ITT population was 5.3 min (3.0, range: <3 to 17) for TachoSil and 9.5 min (8.0, range: <3 to 27) for standard treatment (p < 0.0001; Fig. 2). A significant difference between treatments (p < 0.0001) was also seen in the explorative parametric analysis in which centre effect and interval censoring were taken into account.

3.4. Secondary efficacy end points

Haemostasis was obtained in ≤10 min in 92% (n = 84) of patients in the TachoSil group and in 67% (n = 62) of the standard treatment group (p < 0.0001). A total of 33% of patients in the standard treatment group did not have bleeding controlled after 10 min, and 4% of patients in the group were still bleeding after 20 min.

Haematoma formation on day 2 occurred in 22.5% (20 of 89) of patients in the TachoSil group and in
24.7% (22 of 89) of patients in the standard treatment group. There were no statistically significant differences in the numbers of patients with different size haematomas. Minimal size ≤5 cm in diameter and >5 cm haematomas were seen in 12, 5, and 3 TachoSil patients, and 18, 2, and 2 standard treatment subjects, respectively.

3.5. Exploratory efficacy assessments

There were no differences between treatment groups in terms of postoperative drainage. Average volume of drainage fluid on day 1 was 188 ml for the TachoSil group and 174 ml for the standard treatment group. Blood substitution was performed in three TachoSil and four standard treatment subjects on day 1 after surgery, and in two subjects in each treatment group on day 2. Haemoglobin concentrations in drainage fluid at day 1 were identical at 4.2 g/dl.

TachoSil scored consistently higher than standard treatment in surgeons’ ratings of convenience of preparation, convenience of application, and impression of efficacy. There were no statistically significant differences in laboratory variables or physical signs.

3.6. Safety data

A total of 163 adverse events were reported during the trial. Most of these events were mild (97 events [TachoSil, n = 59; standard treatment, n = 38]) or moderate (51 events [TachoSil, n = 29; standard treatment, n = 22]). Fifteen adverse events were
severe (15 events [TachoSil, \( n = 11 \); standard treatment, \( n = 4 \)]). No subjects withdrew from the trial because of adverse events and no deaths were reported.

A total of 39 events were considered to be related to study treatment (TachoSil: 21 events; standard treatment: 18 events). Two severe adverse events were considered to be related to trial treatment. One of these was extravasation of urine, a nonserious event, in a TachoSil subject, and one was a serious event, subileus, in a standard treatment subject. The patient was treated successfully with analgesics, laxatives, and diet. Both patients recovered fully.

There was no difference between the treatment groups for frequency, severity, and causality of the adverse events. The most frequent adverse events, reported in >3% of patients were constipation, diarrhoea, nausea, pyrexia, postoperative fever, pain, insomnia, extravasation of urine, and hypertension. However, the differences between treatments in the frequency of these events were not statistically significant (Table 3). These adverse events are all recognised as common symptoms of underlying cancer, known complications of nephron-sparing surgery, or aggravation of concomitant illness.

### Discussion

The present trial demonstrates that TachoSil provides a useful adjunctive treatment option to primary haemostasis in NSS. Earlier studies have demonstrated that long-term cancer-free survival after NSS is comparable to that of radical nephrectomy, especially in low-stage renal carcinoma with localised, cortical tumours with a diameter ≤4 cm and with a normal contralateral kidney (elective indication) [1–3,5,17–20] provided a sufficiently large margin of resection [18]. NSS is now an accepted standard of treatment for small, peripherally located kidney tumours. However, control of haemorrhage both during and after this type of surgery remains a challenge, with haemorrhage being a major complication in NSS [21]. Haemostasis is especially important in urologic laparoscopy [22].

The haemostatic efficacy and the safety of TachoSil in kidney resection surgery were clearly demonstrated in the present trial. The primary end point, time to haemostasis, showed TachoSil to be significantly superior to standard treatment for intraoperative control of haemorrhage from the parenchymatous wound following resection of the kidney. This result is supported by the finding that a significantly larger proportion of subjects in the TachoSil group obtained haemostasis within 10 min compared with the standard treatment group. The fact that approximately one third of standard treatment patients did not have bleeding controlled after 10 min has clinical relevance for the surgeon. The use of TachoSil as a local haemostatic thus seems a convenient method for the control of bleeding from the resection surface. The fact that

**Table 3** – Frequency of the most common adverse events (>3% of patients) with \( p \) values of difference between treatment groups

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>TachoSil ( n = 92 )%</th>
<th>Standard treatment ( n = 93 )%</th>
<th>( p ) value of difference Fishers exact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>6.5</td>
<td>2.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3.3</td>
<td>1.1</td>
<td>0.37</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.3</td>
<td>3.2</td>
<td>1.00</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12</td>
<td>7.5</td>
<td>0.33</td>
</tr>
<tr>
<td>Pain</td>
<td>2.2</td>
<td>3.2</td>
<td>1.00</td>
</tr>
<tr>
<td>Postoperative fever</td>
<td>4.3</td>
<td>0</td>
<td>0.06</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.3</td>
<td>3.2</td>
<td>0.72</td>
</tr>
<tr>
<td>Extravasation of urine</td>
<td>3.3</td>
<td>0</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.3</td>
<td>2.2</td>
<td>0.44</td>
</tr>
</tbody>
</table>
none of the secondary end points showed significant results can be attributed to the trial being powered for only the primary outcome variable, time to haemostasis. Thus no conclusive results were to be expected from the secondary efficacy variables, but the consistence of outcome across end points emphasise the haemostatic efficacy of TachoSil in NSS.

Time to intraoperative haemostasis is regarded as a gold standard for the assessment of haemostatic efficacy of fibrin sealants and is recommended by the Food and Drug Administration [23]. This end point has been used in several earlier trials assessing the haemostatic efficacy of surgical drugs and devices in a number of surgical procedures, including renal resection [13,14,24–27]. The method of randomised treatment allocation used in the present study should prevent selection bias by concealment of treatment until the predefined intraoperative eligibility criteria were met. Blinding was not possible because of the nature of treatments. The assessment of haemostasis was equally possible in both treatment groups, since the TachoSil appears semitransparent when moistened and applied on the wound.

The two trial groups were well balanced with regards to demographic and baseline characteristics, such as gender, age, BMI, smoking, alcohol habits, and blood pressure. In addition, the surgical procedures used prior to randomisation were almost identical in the two treatment groups, thus providing the necessary screening balance. This together with the treatment allocation method employed ensures the validity of the study [28].

Surgeons in the study rated TachoSil as superior to standard treatment with regards to convenience of preparation, convenience of application, and impression of efficacy. These ratings confirmed the findings of the primary end point with regards to the haemostatic efficacy of TachoSil patch and highlighted its ease of use, most likely since it needs no preparation prior to application. Although the predecessor of the present trial patch (TachoComb) was previously used successfully in renal surgery [29,30], this is the first multicentre, randomised, controlled trial to demonstrate haemostatic efficacy of a fixed-combination haemostatic patch in renal surgery.

There is a need for efficacious local haemostasis and sealing of kidney resection wounds after NSS. Standard haemostatic suturing is associated with a risk of local ischaemia, which may induce necrosis of the kidney parenchyma and therefore potentially reduce the volume of active nephron tissue. The atraumatic treatment with TachoSil may therefore potentially provide a valuable alternative to standard suturing in patients with only one kidney, where it becomes even more important to preserve kidney parenchyma.

It can be concluded that TachoSil is superior to standard treatment in obtaining intraoperative control of haemorrhage related to NSS of the kidney and may be particularly of value in patients with only one kidney. It should be noted that there was no difference in the frequency of the most common adverse events in the trial. The safety data demonstrate that TachoSil was well tolerated and safe as a haemostatic adjunct treatment. The difference between treatments in time to haemostasis was large enough to have direct clinical relevance for the surgical procedures.

Conflicts of interest

The study was sponsored by Nycomed Denmark and the Department of Urology of the University of the Saarland was reimbursed financially for all expenses made.

References


Editorial Comment on: Efficacy and Safety of TachoSil® as Haemostatic Treatment versus Standard Suturing in Kidney Tumour Resection: A Randomised Prospective Study

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Topical hemostatic agents play a vital adjunctive role in many types of surgery including urologic tumor surgery on the kidney, bladder, and prostate and in various procedures for genitourinary trauma and reconstruction. Perhaps the greatest use to date in urologic surgery has been for partial nephrectomy for management of renal cell carcinoma. The information provided by the authors of the current randomized, prospective, multicenter, and multinational study is both timely and important [1]. The authors compared TachoSil, which is an absorbable equine collagen patch combining human fibrinogen and human thrombin, to standard suturing for hemostasis in patients undergoing partial nephrectomy for resection of small renal cell carcinomas. The agent was safe and the primary end point of time to hemostasis was statistically shorter in the TachoSil patients, \( p < 0.0001 \).

The critical reader should take note of the following points of the trial design to best apply the information to one’s own practice.
All patients had small, superficial tumors that did not extend to the renal collecting system. It would have been helpful if the tumor diameters (range and median) had been given. The fact that temporary vascular occlusion was applied in only 52% and 62% of the TachoSil and standard suture cases, respectively, speaks to the small and superficial extent of the tumors that were selected. All patients in both groups had suture ligation of the “major active arterial and venous bleeder.” There was no use of argon beam or infrared coagulator or laser scalpel. In actual practice one of these adjuncts is used in a high proportion of cases of partial nephrectomy. It would have been surprising if the primary end point of time to hemostasis did not favor the study agent because the design was best possible suture control in both groups and then TachoSil versus no further measures. The subjective impressions of the surgeons in the trial that TachoSil was more convenient and efficient in providing hemostasis must be taken with a grain of salt because it was being compared only to sutures in the other group. Perhaps the authors meant that the TachoSil patch is more rapidly available and convenient to apply than other hemostatic agents, which require warming and mixing (Baxter-Tisseel fibrin sealant with human fibrin, human protein, and bovine fibrinolysis inhibitor) or mixing alone (Baxter-FloSeal gelatin matrix plus human thrombin) at the time of use. The advantage of a ready-made hemostatic patch for use in battlefield trauma victims has been pointed out by military physicians.

The authors are to be congratulated for conducting a prospective, randomized trial that provides initial information on the safety and efficacy of this new topical hemostatic agent, which is available in Europe. To establish the role of this agent in the overall urologic armamentarium, I would look forward to additional trials comparing TachoSil to Tissue and to FloSeal. The role of nephron-sparing surgery both for preservation of renal function as well as oncologic control of renal carcinoma will continue to assume increasing importance. An increasing proportion of smaller tumors will be treated by laparoscopic surgery and an increasing proportion of even larger and more difficult tumors will be treated by open partial nephrectomy. Therefore, topical hemostatic adjuncts that supplement and surpass what can be achieved by suture techniques alone are most welcome.

Reference


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