ABSTRACT

Objectives We aim to quantify the cost difference between patients with incisional cerebrospinal fluid (iCSF) leakage and those without after intradural cranial surgery. Second, the potential cost savings per patient when a decrease in iCSF leakage rate would be achieved with and without added costs for preventative measures of various price and efficacy are modelled.

Design Health economic assessment from a hospital perspective based on a retrospective cohort study.

Setting Dutch tertiary referral centre.

Participants We included 616 consecutive patients who underwent intradural cranial surgery between 1 September 2017 and 1 September 2018. Patients undergoing burr hole surgery or transsphenoidal surgery, or who died within 1 month after surgery or were lost to follow-up were excluded.

Primary and secondary outcome measures Outcomes of the cost analysis include a detailed breakdown of mean costs per patient for patients with postoperative iCSF leakage and patients without, and the mean cost difference. For the scenario analyses the outcomes are the potential cost savings per 1000 patients when a decrease in iCSF leakage would be achieved.

Results Mean cost difference between patients with and without iCSF leakage was €9665 (95%CI, €5125 to €14 205). The main cost driver was hospital stay with a difference of 8.5 days. A 25% incidence reduction would result in a mean cost saving of −€94 039 (95% CI, −€218 258 to −€7077) per 1000 patients. A maximum cost reduction of −€653 025 (95% CI, −€1 204 243 to −€7077) per 1000 patients could be achieved if iCSF leakage would be reduced with 75% in all patients, with a difference of 8.5 days. A 25% incidence reduction to €14 205). The main cost driver was hospital stay and without iCSF leakage was €5125 and without added costs for preventative measures of various price and efficacy are modelled.

Conclusions Postoperative iCSF leakage after intradural cranial surgery increases healthcare costs significantly and substantially. From a health economic perspective preventative measures to avoid iCSF leakage should be pursued.

INTRODUCTION

Cerebrospinal fluid (CSF) leakage is one of the most common complications after neurosurgical intervention. The incidence of CSF leakage after intradural cranial surgery reported in the literature is 8% on average and depends on location of the surgery, indication of the surgery and patient-related risk factors. CSF leakage-related complications include wound infection and meningitis, and may necessitate prolonged hospital admission, external CSF drainage or reoperation. Therefore, CSF leakage is not only associated with substantial morbidity, but also with increased healthcare costs as well. Grotenhuis found that the total extra cost of CSF leakage is approximately €12 000 for intradural cranial surgery, looking at the direct medical costs. Previous research, however, lacks specification of the main cost drivers and analysis of costs for specific treatment modalities for CSF leakage. Both the health and economic consequences of CSF leakage emphasise the importance of prevention of CSF leakage.
Yet, preventative measures to reduce CSF leakage incidence may require financial input as well. Neurosurgeons closing themselves instead of residents, the use of devices, or increased operating room time because of a more precise closing technique to prevent CSF leakage may all lead to increased healthcare costs. Cost-benefit analyses of preventative strategies to reduce CSF leakage are lacking in the current body of literature.

In an increasingly cost aware healthcare system, financial implications of complications and their prevention are of great importance in deciding, which preventative strategies to pursue. Therefore, the health economic consequences should be considered as well when evaluating the efficacy of preventative strategies to avoid iCSF leakage.

The primary objective of the current study is to quantify the difference in healthcare consumption and associated costs between patients with CSF leakage after intradural cranial surgery and those without postoperative CSF leakage. The secondary objective is to quantify the economic effect per patient when a decrease in CSF leakage rate and related complications would be achieved using preventative measures that may require financial input.

**METHODS**

This cost analysis was performed from a hospital perspective, including detailed healthcare consumption of every individual patient. This study uses direct medical costs, without taking into account health insurance reimbursement.

Clinical data from a single centre were retrieved from previously collected retrospective international multicenter database (unpublished raw data). All consecutive adult patients undergoing intradural cranial surgery between 1 September 2017 and 1 September 2018 at the University Medical Center Utrecht were included. Patients who died within 1 month after surgery or were lost to follow-up were excluded, as for these patients there was insufficient certainty regarding the occurrence of the primary outcome measure (CSF leakage) introducing bias into the analysis and healthcare resources used during follow-up. Patients undergoing burr hole surgery or transsphenoidal surgery were excluded, as they represent separate patient categories with specific healthcare utilisation.

The following surgical characteristics had been collected: indication, urgency level, reoperation (yes/no), location of craniotomy (supratentorial or infratentorial), use of dural substitute and use of a dural sealant. Patient characteristics retrieved from the database included: age, sex, preoperative dexamethasone use, history of radiation therapy, diabetes, body mass index and smoking.

CSF leakage was defined as incisional cerebrospinal fluid (iCSF) leakage (either clinically diagnosed or confirmed through Beta-2 transferrin test) and did not include pseudomeningocele. Postoperative infection included superficial wound infection and deep wound infection and/or meningitis requiring treatment. The type of treatment was reviewed when iCSF leakage occurred. The treatment was divided into three categories: conservative treatment, external drainage placement and operative wound revision. Conservative treatment consisted of pressure bandage for wound compression and/or additional suture placement. First, a cost analysis was performed based on clinical and detailed cost data. This cost analysis was followed by scenario analyses to investigate the effect of reduction of iCSF leakage on health economic outcomes. A decision tree was used to combine the afore-mentioned cost analysis and the incidence rates of complications.

**Cost analysis**

Healthcare resources consumed by eligible patients from 30 days prior to 180 days after surgery were retrieved from medical records. Costs included readmissions and considers all-cause healthcare utilisation. Unit prices were retrieved from the Dutch Healthcare Authority (Nederlandse Zorgautoriteit), the cost manual of the National Healthcare Institute (Zorginstituut Nederland) and literature research and linked to the corresponding healthcare activities. The costs for an external ventricle drain and external lumbar drain and dural sealants were based on the existing literature and local prices. Costs for cranial surgery and reoperation were determined based on operating room time multiplied by cost per minute (€10.59). All costs are presented in 2018 Euros.

Outcomes of the cost analysis included a detailed breakdown of mean costs per patient for patients with postoperative iCSF leakage and patients without. Different costs were divided into categories; outpatient visits, diagnostics, primary surgery, expensive drugs (eg, chemotherapy for patients with brain tumour), clinical admissions, other costs (eg, physiotherapy and dietetics), leakage treatment and sealant costs.

As well as the total healthcare costs for patients with CSF leakage stratified by treatment; reoperation, drain (external lumbar drain and external ventricle drain), reoperation and drain, and/or conservative treatment (including pressure bandage and additional sutures). Difference between groups was tested with Mann-Whitney U test since data were not normally distributed.

**Scenario analysis**

**Model development**

A decision tree was developed (online supplemental material 1) outlining intradural cranial surgery and the occurrence of complications, including iCSF leakage. This decision tree allows the quantification of the room for improvement in scenario analyses by adapting probabilities of individual events. This is achieved by multiplying the probability of a patient qualifying for a certain subgroup by the healthcare costs associated with these subgroups, online supplemental material 1 outlines the probabilities and subgroup costs used to recalculate
healthcare costs. Outliers can impact outcomes significantly. To account for input parameter uncertainty distributions were fitted, beta distributions for probabilities and gamma distributions for costs. A probabilistic analysis with a Monte Carlo simulation with 10,000 iterations was used to determine model outcomes and ranges.

**Scenario analyses**

Scenario analyses were performed to determine the health economic effects of reduction of iCSF leakage. Three different scenarios were applied to gain more information on the possible benefits of CSF reduction with various preventative strategies. (I) The iCSF leakage incidence use was decreased with 25% steps between 0% and 75%. (II) The iCSF leakage incidence was reduced and weighted against varying costs of potential interventions of variable efficacy. (III) The first two scenario's applied for subgroups with different risk of iCSF leakage (supratentorial surgery and infratentorial surgery). Outcomes of the scenario analyses were presented as difference in costs and number of iCSF leakage cases avoided per 1000 patients was calculated as well as the number needed to treat (NNT). To determine parameter influence on the outcome of the scenarios, a deterministic sensitivity analysis was performed and a tornado diagram was constructed.

**RESULTS**

In total, 616 consecutive patients were included in this study. Table 1 provides an overview of the patient characteristics. The mean age of patients was 53.5 (±15.8) years. The most common indication for surgery was tumour resection; 399 patients (64.8%) and most patients had a supratentorial approach; 517 (83.9%). A total of 59 patients had postoperative iCSF leakage (9.6%).

### Cost per patient and detailed breakdown costs

Average cost per patient and a detailed breakdown of costs are included for all of the 616 patients. In table 2, the average costs per patient with and without iCSF leakage are outlined. Five out of seven cost categories were higher for patients with iCSF leakage compared with patients without iCSF leakage. Costs for external ventricle drain, external lumbar drain and reoperation were categorised under treatment costs in table 2.

Difference in costs between patients without iCSF leakage and with iCSF leakage was €9665 (95% CI, €5125 to €14,205). Total average healthcare costs for patients without iCSF leakage was €20,498 (95% CI, €19,183 to €21,813) compared with €30,163 (95% CI, €23,654 to €36,672) for patients with iCSF leakage (table 2).

When comparing costs incurred starting from the day of primary surgery (days 0–180), costs were €17,759 (95% CI, €16,497 to €19,021) for patients without iCSF leakage and €28,105 (95% CI, €21,695 to €34,515) for patients with iCSF leakage.

The main reason for the difference in cost, over both the total time and the postoperative time, was the significant difference in length of hospital stay, for which costs are categorised as clinical admissions. Difference in length of stay (LOS) was 8.5 days (95% CI, 5.3 to 11.7). For patients without incisional leakage, LOS was 12.8 days (95% CI, 11.9 to 13.8) and for patients with iCSF leakage LOS was 21.3 days (95% CI, 16.6 to 26.1). Furthermore, the incidence of secondary complications was significantly higher in the iCSF group. Highest costs among subgroups were found for patients with deep wound infection and/or meningitis (€39,323 to €57,862). Patients without additional complications had the lowest costs among all subgroups (€19,050 to €26,797) (table 3).

For supratentorial surgery, there was a significant cost difference between patients with iCSF leakage (€20,180,
### Table 2 Healthcare costs for patients with and without iCSF leakage and the difference (N=616)

| Scenario | No iCSF leakage (N=557) | iCSF leakage (N=59) | Difference | P value |
|----------|-------------------------|---------------------|------------|---------|
|         | Mean (95% CI)           | Mean (95% CI)       |            |         |
| Primary surgery | €1958 (€1882 to €2035) | €2439 (€2102 to €2776) | €481 | 0.007  |
| Out patient visits | €1696 (€1570 to €1821) | €2006 (€1631 to €2380) | €310 | 0.132  |
| Diagnostics | €2360 (€2215 to €2505) | €2903 (€2214 to €3592) | €543 | 0.032  |
| Expensive drugs | €948 (€572 to €1324) | €812 (€135 to €1489) | −€136 | 0.821  |
| Clinical admissions | €10 701 (€9806 to €11 597) | €17 568 (€12 642 to €22 494) | €6867 | 0.004  |
| Others | €2703 (€2377 to €3030) | €3844 (€2638 to €5050) | €1141 | 0.06   |
| Leakage treatment | €0 (€0 to €0) | €474 (€354 to €595) | €474 | <0.001 |
| Sealant | €131 (€116 to €146) | €117 (€72 to €161) | −€14 | 0.555  |
| Total | €20 498 (€19 183 to €21 813) | €30 163 (€23 654 to €36 672) | €9665 | 0.005  |

Others includes physiotherapy and dietetics. P values smaller than 0.05 are considered significant. iCSF, incisional cerebrospinal fluid.
outcomes was costs for patients without iCSF leakage and an infratentorial approach. Lowest influence was found for the incidence of iCSF leakage in infratentorial patients (figure 3).

**DISCUSSION**

There is a substantial and significant cost difference of €9665 between patients with postoperative iCSF leakage after intradural cranial surgery and those without. The average healthcare cost for cranial intradural surgery ranges between €20 498 for patient without iCSF leakage and €36 117 for patients with reoperation, which was the most expensive. A maximum cost reduction of €653 025 (95% CI, −€1 204 243 to −€169 120) per 1000 patients could be achieved if iCSF leakage would be reduced with 75% in all patients.

Our model shows that reducing leakage rates could lead to substantial cost reduction, even if financial input is required. However, whether the use of preventative measures that require financial input in all patients or a subgroup of patients at risk results in cost savings depends on their price and efficacy. Because of the higher risk of iCSF leakage in infratentorial surgery, more expensive preventative measure of a certain efficacy could still lead to cost savings in this subgroup, when they do not for the total population.

To our knowledge, this is the largest cost analysis providing a detailed breakdown of costs for iCSF leakage after intradural cranial surgery. Furthermore, it is the first study applying a model to calculate the health economic effects of improved preventative measures. An advantage of the method applied in this study is the adaptability of the transparent model to other settings. If other hospitals are aware of their leakage rate and healthcare costs, this method could be used to estimate possible future cost savings, for example with improved sealants.

One limitation of our approach is the effect of initial surgery costs on the results of our analyses. Despite this being the most comprehensive method of taking into account all associated costs, it may be the case that part of the cost difference is driven by the initial surgery, as complex and longer surgeries are more expensive. Second, we have collected healthcare consumption in a single centre. There is thus a theoretical risk of missing the costs of patients that may have received follow-up treatment elsewhere, without this being communicated to the primary centre. As patients with loss to follow-up were excluded from the initial database and treatment of complications in a different centre is unusual, we do not believe this has affected the outcomes of the current study.

Thereby, although this analysis contains the largest patient population in an economic evaluation of iCSF leakage, the number of patients in the individual categories for secondary complications and treatment modalities remains low. It is, therefore, difficult to interpret cost differences for specific secondary complications in detail. In these limited numbers of cases, heterogeneity of patients could be the main difference between those with iCSF leakage and those without. Results of the comparisons between the different treatment modalities should be interpreted with some caution as well, for the same reason. Especially, the subgroup of patients who underwent reoperation is limited in size and has large SD of both the LOS and the costs. Furthermore, these limited subgroups led to larger uncertainty around the scenario analyses modelling the potential health economic effects of iCSF leakage reduction, especially for the infratentorial subgroup. Another limitation of the scenario analyses is the linear reduction in iCSF leakage, which assumes that iCSF leakage can be prevented with a certain efficacy across the total population. It may, however, be the case that for certain subgroups iCSF leakage cannot be avoided with preventative measures.

These results are based on healthcare consumption and costs of one centre in the Netherlands. Therefore, applying these results to different countries is challenging. Differences in clinical practice and prices, for
Table 4  Total healthcare costs and LOS for patients with iCSF leakage stratified by treatment

| Treatment               | N  | Mean costs € | Costs SD € | Mean LOS (days) | LOS SD | P value | Conservative versus surgery | Conservative versus surgery+drain | Conservative versus drain | Surgery versus surgery+drain | Surgery versus drain | Surgery+drain versus drain |
|-------------------------|----|--------------|------------|----------------|--------|---------|---------------------------|-----------------------------|-----------------------|-----------------------------|-----------------------|---------------------------|
| Conservative treatment  | 18 | €21 046      | €11 433    | 11.3           | 6.8    | 0.976   | 0.027                     | -0.001                     | 0.463                 | 0.450                     | 0.327                 |
| Surgery                 | 7  | €36 117      | €45 056    | 26.1           | 36.7   | 0.027   | <0.001                    | 0.463                     | 0.450                 | 0.327                     |
| Surgery+drain           | 8  | €36 007      | €21 490    | 26.5           | 22.1   | <0.001  | 0.463                     | 0.450                     | 0.327                 |
| Drain                   | 26 | €33 073      | €25 544    | 19.9           | 16.1   | 0.495   | 0.015                     | <0.001                    | 0.232                 | 0.531                     | 0.270                 |
| All patients (N=59)     |    | €30 163      | €24 977    |                |        |         |                           |                           |                       |                            |

P values smaller than 0.05 are considered significant.
iCSF, incisional cerebrospinal fluid; LOS, length of stay.

Table 5  Results of the scenario analysis: difference in healthcare costs and cases avoided per 1000 patients and number needed to treat to prevent one iCSF leakage case

| Scenario          | Incidence change | Difference in healthcare costs per 1000 patients | Cases of iCSF leakage avoided per 1000 |
|-------------------|------------------|--------------------------------------------------|----------------------------------------|
|                   | Mean 95% CI      | % runs saving*                                   | Mean 95% CI NNT                        |
| All patients      |                  |                                                  |                                        |
| 1                 | −25%             | −€216 609 to −€420 445                          | 99.71% 24                             | 18.45 to 30.00 42   |
| 2                 | −50%             | −€434 882 to −€821 229                          | 99.61% 46                             | 37.16 to 59.91 21   |
| 3                 | −75%             | −€653 025 to −€1 204 243                         | 99.73% 72                             | 54.97 to 89.89 14   |
| Supratentorial only| −25%             | −€193 849 to −€371 531                          | 99.83% 18                             | 12.58 to 23.23 57   |
| 2                 | −50%             | −€387 929 to −€746 597                          | 99.83% 35                             | 25.00 to 46.33 29   |
| 3                 | −75%             | −€580 844 to −€1 112 175                         | 99.87% 53                             | 37.44 to 69.81 19   |
| Infratentorial only| −25%             | −€342 726 to −€1 095 834                        | 85.38% 57                             | 37.58 to 79.55 17   |
| 2                 | −50%             | −€681 934 to −€2 035 623                        | 84.81% 115                            | 76.19 to 160.71 9   |
| 3                 | −75%             | −€1 036 407 to −€3 276 620                      | 85.24% 172                            | 114.64 to 240.03 6   |

*Percentage of Monte Carlo simulations, percentage of runs out of 10 000, in which the scenario was cost saving compared with current standard care.
iCSF, incisional cerebrospinal fluid; NNT, number needed to treat.
instance, may influence the effects observed in this study considerably.\textsuperscript{7} It is thus recommended that data on cost prices and resource use should be obtained from or adapted to the setting of interest.\textsuperscript{7} Furthermore, baseline risk should be location specific, whereas treatment effect may be more generalisable.\textsuperscript{7} Although, larger differences to be expected between the healthcare systems across continents, even within western Europe economic analyses of medicines vary significantly.\textsuperscript{7}

The additional healthcare costs for patients with incisional CSF leakage in this study are comparable to those found by Grotenhuis in the Netherlands, who found a cost difference of approximately €12 000, for cranial surgery including transsphenoidal procedures.\textsuperscript{4} Our study includes all healthcare resources consumed within a predefined time frame, whereas Grotenhuis based calculations on certain cost categories only. Another study from Germany by Piek \textit{et al} calculated cost differences between patients with and without CSF leakage in detail and found a comparable result of €11 420.\textsuperscript{8} Their study, however, also included subcutaneous CSF collections as CSF leaks, and it has a limited sample size of 168 patients (of which only three had percutaneous CSF leaks).\textsuperscript{8}

The breakdown of costs shows that clinical admission is the main cost driver for the difference between patients with and without iCSF leakage. Patients with iCSF leakage have higher risk of infection or meningitis.\textsuperscript{9} These complications may further explain the cost difference between patients with and without iCSF leakage as they require prolonged clinical admission. These results are in line with the study of Parikh \textit{et al} that identified increased LOS and the association of CSF leakage with secondary complications such as meningitis as the main reasons for increased healthcare costs after transsphenoidal surgery.\textsuperscript{10}

Additionally, the costs for interventional treatment of iCSF leakage are a substantial cost driver, considering that patients who can be managed conservatively have total average costs that are comparable to patients without iCSF leakage. In the group of patients managed conservatively, though, 10/18 patients (55.6%) did not have continuous iCSF leakage, but incisional leakage that occurred once or twice, suggestive of a subcutaneous pocket that has discharged. All patients that had to be managed with invasive treatment had continuous iCSF leakage. Patients treated with an external CSF drain have significantly longer LOS and higher costs compared with those treated conservatively. Contrary to Parikh \textit{et al} we did not find shorter LOS in patients treated with reoperation compared with those treated with external CSF drainage only.\textsuperscript{10} This may imply that reoperation as a treatment for iCSF leakage is performed sooner after endoscopic endonasal surgery than after craniotomy. An advantage of reoperation compared with external CSF drainage is the quick return to mobilisation as opposed to bedrest required during external CSF drainage. This is not reflected in a difference in LOS between these patients in our population, however. Besides a delay in surgical treatment, other factors related to recovery such as comorbidity may explain why LOS is similar for these treatment modalities.

This study confirms that from a health economic perspective, iCSF leakage should be reduced. Improved preventative strategies reducing the iCSF leakage rate, even though they may add to the overall healthcare costs per patient, could be beneficial from an economic standpoint. Furthermore, increased understanding of risk factors for iCSF leakage and associated costs may contribute to improving the indication for use of currently available and future methods of augmented dural closure. Considering that conservative treatment for continuous iCSF leakage is rarely effective, early interventional treatment for this group is recommended.
Furthermore, methods that shorten LOS for patients with external CSF drains should be investigated. Our model of the health economic effects of iCSF leakage and potential cost savings of improved preventative strategies should be applied to different healthcare settings to evaluate the cost difference and potential cost savings location specifically to assist physicians and healthcare managers in decision-making regarding preventative strategies to avoid iCSF leakage in their situation.

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