

Serious Complications Associated with External Intrathecal Catheters Used in Cancer Pain Patients

A Systematic Review and Meta-analysis

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Background: Potential risks of intrathecal catheters in cancer patients include infection, bleeding, and neurologic injury.

Methods: A systematic review and a pooled analysis of observational studies were performed. Articles reporting on adverse events (infections, bleeding, granuloma, and death) associated with intrathecal catheters and external pumps in cancer patients were identified. Electronic searches of PubMed, MEDLINE, and EMBASE were conducted. Observations from different studies were pooled using a generalized mixed-effect model. Model estimates and their standard errors (SEs) were used for calculating 95% confidence intervals (CIs) on the overall proportion.

Results: The analysis identified 10 articles, including a total of 821 patients. Twenty catheter-related infections were identified. Of these, 10 were superficial and 10 were deep infections, with rates of 2.3% (95% CI, 0.8–6.1) and 1.4% (95% CI, 0.5–3.8), respectively. Furthermore, the authors calculated that every 71st patient had a deep infection after an average catheter duration of 54 days. The risk of bleeding was found to be 0.9% (95% CI, 0–2.0), and for neurologic injury 0.4% (95% CI, 0–1.0). The infection rates are comparable to other intrathecal catheter techniques.

Conclusions: Serious complications are rare in both hospitalized and homebound patients with intrathecal catheters. This analysis supports the reasoning that the potential benefit of intrathecal catheters in the treatment of severe cancer pain is likely to outweigh the potential for serious complications associated with this technique. Therefore, an external intrathecal catheter can be considered an effective and low-cost solution for the control of pain in such patients.

THE vast majority of patients with cancer pain can be satisfactorily treated according to conservative methods such as the three-step analgesic ladder approach, developed by the World Health Organization.¹ Nevertheless, in some patients pain relief is insufficient or the side effects of the chosen analgesic regimen are unbearable, prolonging suffering from severe pain. In such cases, invasive procedures, including the placement of a chronic indwelling intrathecal catheter, may be helpful.² If intrathecal or epidural catheters are in place for 3 or more months, implantable programmable infusion pumps (internal system) seem to be the most cost-effective approach.³

For patients with a catheter duration of less than 3 months or having an unknown life expectancy, the easiest and most cost-effective way is the tunnelled subcutaneous catheter with an external infusion pump system.^{1,4}

Infections are a potential risk of intrathecal or epidural catheters.⁵ A recent meta-analysis⁶ of chronic indwelling epidural catheters revealed that 1 in every 35 patients with a chronic indwelling epidural catheter in place for an average of 74 days will develop a deep epidural infection. One in every 510 patients will die of deep epidural infections.⁶ Further potential risks of these minimally invasive intrathecal procedures include bleeding and neurologic injury. Rates of complications associated with short-term use of epidural catheters in obstetrics have been calculated. Epidural hematomas occur in 1 in every 168,000 women, persistent neurologic injury occurs in 1 in every 240,000, and transient neurologic injury occurs in 1 in every 6,700.⁷ The duration of catheterization in obstetrics is rarely longer than 1 day, whereas in cancer patients catheters may be in place for months. Furthermore, obstetric patients are generally young and in good physical condition, whereas cancer patients often have severe illnesses, which are frequently accompanied by coagulation disorders and immune suppression. Similar data about complication rates in chronic indwelling intrathecal catheter systems are available⁸ but are consistently restricted to internal catheter systems or port systems.

The clinical decision to implant an intrathecal catheter is, however, influenced by the predicted benefit as well as the risk of complications. Therefore, in the current study we looked for robust estimates of infection, bleeding, neurologic injury, and catheter-associated death in cancer patients that have been linked to intrathecal catheters with external pumps in place for longer than 7 days.

Materials and Methods

The outcomes defined in our study protocol were deep and superficial infections, bleeding, neurologic injuries, granuloma, and death associated with intrathecal catheters with external pumps in cancer patients. Patients with noncancer pain were excluded because they generally do not have long-term external pumps and are more likely to have different immunocompetencies. Articles reporting on adverse events associated with intrathecal catheters and external pumps in cancer patients were identified using two different approaches. Initially, electronic searches of PubMed (from 1966), MEDLINE

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(from 1966), and EMBASE (from 1980) up through August 2007 were conducted with no language restrictions applied. The searches combined controlled vocabulary and free text terms for both the intervention (intrathecal catheter) and the outcome (adverse effect). Details of the terms used are shown in the appendix. Subsequently, reference lists of reviews and retrieved studies were reviewed for additional studies. Where necessary, authors were contacted to obtain further detailed information.

The titles and abstracts of all retrieved articles were read (D.A.), and those of no clear relevance were eliminated. Full copies of all the remaining studies were obtained and read independently (D.A. and W.R.). In case of interrater variability, D.A. and W.R. discussed the differences and made a joint decision. Those reporting quantitative data for serious adverse events such as infection using the infection criteria used by the original authors (deep and superficial), bleeding, neurologic injury (persistent, transient, and of unknown duration), granuloma, or death associated with the intrathecal catheter system were included in an initial list of studies. We then selected those reporting at least 20 patients, with a median catheter duration of at least 7 days, quantitative data for the previously mentioned serious adverse events, and an external catheter system. Port-a-cath-based systems were excluded.

Statistical Analyses

Information about the type of study, patients, intervention, and numbers of individuals experiencing adverse outcomes was tabulated. Quality of Reporting of Meta-analyses rules⁹ were followed where applicable. It was our intention to pool results and to calculate complication rates separately. Information on infections is presented in two ways: (1) the percentage of patients with deep, superficial, or any catheter-related infection and (2) the incidence of infections per 1,000 catheter treatment days. The amount of total catheter days of a single study was either taken from the text (if indicated) or calculated by multiplying the number of patients by the mean (or median) catheter duration of this study.

Observations from different studies were pooled using a generalized mixed-effect model with a logit link function with a random effect accounting for the individual studies. Model estimates and their SEs were used for calculating 95% confidence intervals (CIs) on the overall proportion. All analyses were performed using R Development Core Team (Foundation for Statistical Computing, Vienna, Austria).¹⁰ Statistical table calculations were performed with Microsoft Excel version 2002 SP3 (Microsoft Corporation, Redmond, WA).

Results

The electronic search (appendix) and review of reference lists of the electronically identified articles led to the

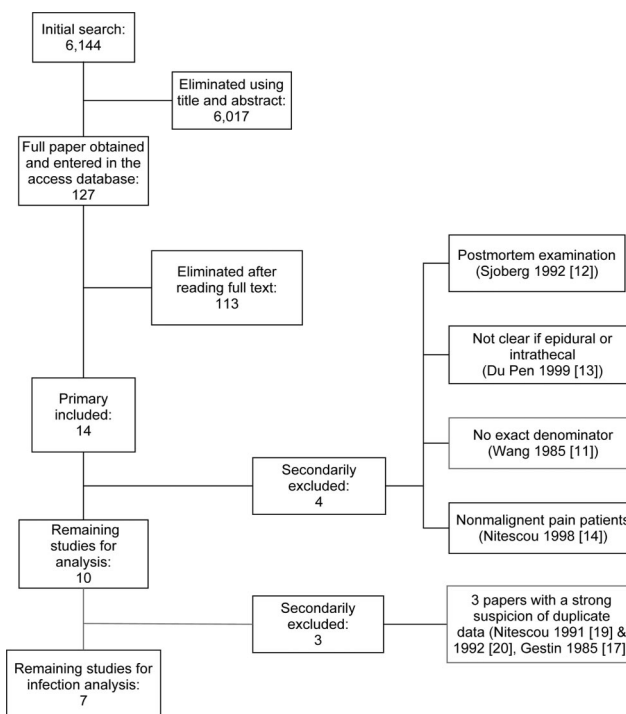


Fig. 1. Search results for infection analysis.

identification of 6,144 articles (fig. 1). The results of this initial search were reduced to 127 articles after reviewing the titles and abstracts. These 127 were read entirely; 14 of them met the inclusion criteria.

Of these, one study¹¹ was excluded because the five infections described were not assigned to one of the three groups (single injections, external catheter, or implanted pumps). Three other articles had to be excluded: One examined the patients postmortem,¹² one article did not distinguish between epidural and intrathecal infections,¹³ and another investigated noncancer patients.¹⁴ Three of the remaining 10 articles originated from the same authors. Therefore, we attempted to find out whether these three articles reported on the same patients. Two of these had no overlap in their patient reporting. One¹⁵ reported on the period from 1983 to 1988; the other¹⁶ reported on the period from 1988 to 1991. The third article¹⁷ was probably part of an article published 1 yr later¹⁸ and, therefore, was excluded from our meta-analysis. Another two articles^{19,20} were part of a larger overview²¹ and were also excluded from our meta-analysis. Two authors were contacted for more detailed information. However, we received no reply.

In summary, 10 of the remaining articles, including a total of 821 patients, were used for the comprehensive meta-analysis (table 1). Three articles^{17,19,20} were excluded because of potential overlap of data. Seven^{15,16,18,21–24} of these, including 560 patients, were used in the infection rate analysis (table 2).

Of the definitively included articles (infection, neurologic injury, bleeding, and granuloma), 33% were identified by

Table 1. Study Details

Reference	Type of Article	Patients Included	No. of Patients (or Catheters)	Technique	Duration of Catheter	Results	
						Adverse Events	Comments
Baker <i>et al.</i> , ²² 2004	Retrospective study	Cancer patients	76 (81)	Since 1996, 96% of catheters were tunneled 1/3 Thoracic level	Up to 547 days Median duration from 1996 to 2002: 24 days	Superficial infections: 5 Deep infections: 2 (meningitis (one died)) Postspinal cord compression: 2 (granuloma?)	81 catheters were performed in 76 patients Not clear whether postspinal cord compression provoked neurologic injury; also not clear why spinal cord compression occurred (granuloma? bleeding?)
Crul <i>et al.</i> , ¹⁵ 1991	Not clear	Cancer patients	30	All patients with tunneled catheters and suture on the fascia of the paraspinal musculature	Not clear because epidural and intrathecal catheters are mixed for the treatment duration calculations (10–366 days)	Superficial infections: 2	Discrepancy of the superficial infection figure between the text and the table of the article: table indicates 2, text 1 superficial infection
Devulder <i>et al.</i> , ²³ 1994	Prospective study	Cancer patients	33	Intrathecal catheter	< 22 days: 10	Deep infections: 0 Superficial infections: not mentioned	Observation period: 1983–1988 Probably most of the patients reconnected the system after an incidental disconnection, so this could be the reason for the high infection rate
Gestin <i>et al.</i> , ¹⁷ 1985	Not clear	Cancer patients	35, all outpatients	Ten patients with intermittent bolus, the other 23 with continuous patient-controlled analgesia	22–90 days: 11, > 90 days: 12	Deep infections: 3 (meningitis) Postoperative hemorrhage (unclear where; subcutaneously?)	3 patients had to change their catheter, so in total 38 catheters
				Bolus injections of morphine via a tunneled catheter in a closed device twice a day	5 patients less than 10 days, maximum 240 days	Superficial infection: 1 patient with fever and a positive culture of the entry site (<i>restitutio ad integrum</i> , catheter not taken away)	
Gestin <i>et al.</i> , ¹⁸ 1986	Retrospective study	Cancer patients	115 (6 dropouts), 80% outpatients	More than 4,000 bolus injections in total	In total 2,016 catheter days	Deep infections: none mentioned, so probably no deep infections	2 respiratory depressions due to handling errors (10-fold too high doses); outcome <i>restitutio ad integrum</i> Observation period: April 1979 to April 1985
				Bolus injections of morphine via a tunneled catheter in a closed device twice a day More than 15,000 bolus injections in total	Mean follow-up 68 days, max duration 13 mo	Superficial infections: probably 0, but no explicit information Deep infections: 4 (2 due to negligence, 2 others [immunosuppression]) Every 1,955th infection = 3.5% infection rate	
Gestin <i>et al.</i> , ²⁴ 1997	Retrospective study	Cancer patients	50	Tunneled catheter	Mean follow-up 142 days (7–584)	Superficial infections: 0	Observation period: 1991–1994
				External pump with patient-controlled boluses and continuous infusion	In total 5,602 morphine therapy days	Deep infections: 0	
Nitescu <i>et al.</i> , ¹⁹ 1991	Not clear	Cancer patients	142 (157 catheters)	Catheters were tunneled subcutaneously	Greatly exceeding 10,000 catheter days	Superficial infections: 1, due to suture abscess	Observation period: 1985–1990
					Mean 72 days 1–525 days	Deep infections: 1 meningitis (survived another 179 days with the same catheter; infection occurred 153 days after insertion of the catheter) Bleeding in the tunnel: 1 No neurologic injury	

(continued)

Table 1. Continued

Reference	Type of Article	Patients Included	No. of Patients (or Catheters)	Technique	Duration of Catheter	Results	
						Adverse Events	Comments
Nitescu <i>et al.</i> , ²⁰ 1992	Prospective cohort study	Cancer patients (n = 81)	89 patients	Percutaneous catheter	Overall duration unknown	Superficial infections: 1 (nonmalignant pain patient) Deep infections: 1 (the same patient)	Observation period: 1987–1991 Study was designed to find recommendations on the exchange of containers (syringes and cassettes) and antibacterial filters The patient with deep infection developed meningitis from the infected breakdown of skin
Nitescu <i>et al.</i> , ²¹ 1995	Prospective cohort study, nonrandomized	Noncancer patients (n = 8)	200 (79 outpatients)	Externalized tunneled catheter	1–575 days (median 33)	Superficial infection: 1 patient	Observation period: December 1985 to January 1991
		Cancer patients (n = 200)		Intermittent and continuous	Cumulative total of 14,485 days	Deep infections: 0 epidural abscess, meningitis 1 patient (= one in 40 years of treatment) Bleeding in the tunnel: 1 patient (not extensively, stopped by compressive dressing) Neurologic complications: 5 patients	200 cancer patients with 223 catheters
Van Dongen <i>et al.</i> , ¹⁶ 1993	Retrospective study	Cancer patients	51	Catheters were tunneled subcutaneously over a distance of 30–40 cm	Total treatment duration: 3,140 days	Superficial infections: 2 Deep infections: none No respiratory depression No neurologic sequelae	Observation period: 1988–1991
Sjoberg <i>et al.</i> , ¹² 1992			15	Tunneled catheter	4–274 days, mean 81 days	Superficial infection: 0	Excluded because results based on postmortem examinations
Du Pen, ¹³ 1999	Probably retrospective	Cancer patients	75	Unclear		Epidural granulations: 2 2 infections (deep? superficial? epidural? intrathecal?)	Excluded because unclear whether epidural or intrathecal
Nitescu <i>et al.</i> , ¹⁴ 1998	Prospective cohort study	Nonmalignant pain patients	90 (106 catheters)	External tunneled catheter connected to an external pump with basic rate Possibility of “patient-controlled analgesia” mode (boluses: 1–4 times an hour)	3–1,706 days (median 60 days) Cumulative total of 14,686 days, 7,460 (50%) of which were spent at home	Transient paresthesiae (n = 26), short-lasting pareses (n = 16) No neurologic sequelae Superficial infection: probably none, but not explicitly mentioned Deep infections: 4 (meningitis) Attempted suicide (n = 5, 3 of which were successful) No death attributed	Bradypnea: 1 patient Observation period: 1987–1995 Excluded due to patients with nonmalignant pain

going through reference lists and 67% were identified by computer search. Three articles,^{20,21,23} with a total of 322 patients, were prospective and accounted for 30% of the included articles. Four articles,^{16,18,22,24} with a total of 292 patients, were retrospective and accounted for 40% of the included articles. The type of study was either unclear or not mentioned for the remaining articles,^{15,17,19} which included 207 patients (30% of the included articles).

Deep, Superficial, and Any Catheter-related Infections

The seven articles^{15,16,18,21–24} included in the infection analysis received a total of 560 patients and re-

ported on 10 deep infections (infection rate, 1.4%; 95% CI, 0.5–3.8). That is, the analysis of these seven articles suggests that every 72nd patient will develop a deep infection. In two articles,^{15,23} it was not possible to derive the total duration of catheter placement. Apart from these two articles, the other five accounted for a total of 26,604 catheter days, of which we could calculate a deep infection risk of 0.212 cases per 1,000 catheter days (95% CI, 0.073–0.62). Namely, only a single deep infection will result after an estimated 4,716 catheter days (95% CI, 1,613–13,699) (tables 2 and 3). We detected seven infections in 497 cases, which accounted for a total of 26,604 catheter days. Therefore, every 71st patient had a

Table 2. Detailed Results for Infections from Individual Studies

Study	Cohort	No. of Patients or Catheters	Catheter Duration	Catheter Duration in Total	Deep Infections			Superficial Infections			Any Catheter-related Infections		
					Amount of Infections	Percent of Patients Affected	Per 1,000 Catheter Days	No. of Infections	Percent of Patients Affected	Per 1000 Catheter Days	No. of Infections	Percent of Patients Affected	Per 1,000 Catheter Days
Baker <i>et al.</i> , ²² 2004	Retrospective	81	Up to 547 days, mean 24 days	1,944	2	2.5	1.0	5	6.2	2.6	7	8.6	3.6
Crui <i>et al.</i> , ¹⁵ 1991	Unclear	30	10–366 days	Unclear	0	0	No data	2	6.7	No data	2	6.7	No data
Devulder <i>et al.</i> , ²³ 1994	Prospective	33	Unclear	Unclear	3	9.1	No data	No data	No data	No data	3	9.1	No data
Gestin <i>et al.</i> , ¹⁸ 1986	Retrospective	115	Mean 68 days	7,820	4	3.5	0.5	No data	No data	No data	4	3.5	0.5
Gestin <i>et al.</i> , ²⁴ 1997	Retrospective	50	Mean 142 days	7,100	0	0	0	0	0	0	0	0	0
Nitescu <i>et al.</i> , ²¹ 1995	Prospective	200	1–575 days, median 33 days	6,600	1	0.5	0.2	1	0.5	0.2	2	1.0	0.3
Van Dongen <i>et al.</i> , ¹⁶ 1993	Retrospective	51	3,140 catheter days	3,140	0	0	0	2	3.9	0.6	2	3.9	0.6
Patients in studies reporting the outcome		560			10.0			10.0			20.0		
Risk (95% confidence interval), %						1.4 (0.5–3.8)			2.3 (0.8–6.1)			2.9 (1.1–7.4)	
Calculable catheter duration in total			26,604 days	26,604	26,604			18,784			26,604		
Infections usable for catheter duration calculations					7			8			15		
Risk per 1,000 catheter days							0.212			0.308			0.412

deep infection after an average catheter duration of 54 days. Only one article²¹ indicated that the deep infection case described in the article occurred after 145 catheter days (the superficial infection case occurred after 130 catheter days). Of the other articles, we are unaware of the time at which infections occurred.

Five articles,^{15,16,21,22,24} accounting for 412 cases, report on 10 superficial infections (infection rate, 2.3%; 95% CI, 0.8–6.1). In one¹⁵ of these five articles, it was not possible to derive the duration of catheter placement. Excluding this article, we calculated a superficial infection risk of 0.308 cases per 1,000 catheter

days from a total of 18,784 catheter days (95% CI, 0.105–0.898). Again, this means that a single superficial infection will occur only after approximately 3,247 catheter days (95% CI, 1,114–9,524) (tables 2 and 3).

All seven articles^{15,16,18,21–24} report on a total of 20 any catheter-related infections (infection rate, 2.9%; 95% CI, 1.1–7.4). In two articles,^{15,23} it was not possible to derive the total duration of catheter placement, resulting in a total of 26,604 catheter days (based on five remaining articles). In addition, we calculated an “any catheter-related infection” risk of 0.412 cases per 1,000 catheter days (95% CI, 0.141–1.204). Therefore, a single “any catheter-related infection” will occur only every 2,427 catheter days (95% CI, 831–7,092) (tables 2 and 3).

Most of the articles included in this analysis used a tunnelled catheter; in one article,²³ it was unclear whether a tunnelled catheter was used.

Bleeding

Three studies,^{19,21,23} including a total of 375 patients, report on bleeding and hematoma. Because of the likelihood that two studies^{19,21} mentioned the same case, we counted two cases out of 233 patients accounting for at least 6,660 catheter days: one post-operative bleeding²³ and one bleeding in the tunnel.²¹ In one study,²³ the total catheter days remained unclear. The risk is 0.9% (95% CI, 0–2.0) or a single case of bleeding after 3,330 catheter days. No neurologic

Table 3. Summary of Infection Rates

	Site of Infection		
	Deep	Superficial	Any Catheter Related
Number of studies	7	5	7
Number of patients with infections	10	10	20
Total number of patients	560	412	560
Percentage of patients with infection	1.4	2.3	2.9
Risk of infection per 1,000 catheter days	0.212	0.308	0.412
Mean number of days of catheter use before one infection occurs	4,716	3,247	2,427

If catheter days were missing, the corresponding infection numbers were not included in the calculation of risk of infection per 1,000 catheter days.

Table 4. Detailed Information on Risk of Bleeding, Neurologic Injury, and Death

Study	No. of Patients or Catheters	Catheter Duration	Bleeding	Neurologic Injuries	Deaths
Baker <i>et al.</i> , ²² 2004	81	< 547 days; mean 24 days		2 spinal cord compressions (granuloma? bleeding?)	3 respiratory arrests
Devulder <i>et al.</i> , ²³ 1994	33	Unclear	1 postoperative hemorrhage (unclear where)		
Gestin <i>et al.</i> , ¹⁸ 1986	115	Mean 68 days			2 respiratory depressions due to handling errors (10-fold too high doses); outcome <i>restitutio ad integrum</i>
Nitescu <i>et al.</i> , ¹⁹ 1991	142		Bleeding in the tunnel: 1	No neurologic injuries	
Nitescu <i>et al.</i> , ²¹ 1995	200	6,600 days	Bleeding in the tunnel: 1 patient (not extensively, stopped by compressive dressing), probably the same patient as in Nitescu <i>et al.</i> , ¹⁹ 1991	Neurologic complications: 5 patients	
Van Dongen <i>et al.</i> , ¹⁶ 1993	51	3,140 catheter days		No neurologic sequelae	No respiratory depression

injuries were mentioned in the context with these two cases of bleeding (table 4).

Neurologic Injury

Two articles^{16,19} reported no neurologic injuries. One article²¹ reported five neurologic injuries, in which all five patients had either tumor masses in the epidural space, extensive metastases of the vertebral column, or compression fractures. Another article²² reported on two postspinal cord compressions but provided no further detail (*e.g.*, on tumor compression or bleeding). Neurologic injuries occurred at most twice in 474 patients (risk, 0.4%; 95% CI, 0–1.0) (table 4).

Granuloma

No reports on granuloma were found in the included articles. One postmortem pathoanatomical and, thus, excluded study¹² including 15 patients reported on two intrathecal granulomas (risk, 13%; 95% CI, 0–31) (table 4).

Death

No information on the incidence of death was retrieved from the included articles. One article¹⁴ reported on two cases of respiratory depression without severe consequences, one article²² reported on three respiratory arrests without further information on ongoing development, and another¹⁶ reported on no problems with respiratory depression in the context of intrathecal catheters (table 4).

Discussion

Epidural and intrathecal catheters are well-established techniques to reduce cancer pain.^{22,25} The most widely accepted indications for intrathecal analgesia in cancer pain patients include unacceptable side effects of the systemic pain therapy (mostly opioid therapy) or unsuccessful/insufficient therapy with opioids despite increasing doses.²⁶

Long-term intrathecal morphine infusions seem to provide satisfactory analgesia, have few associated side effects, and permit a high degree of patient autonomy.²⁴ According to Kedlaya *et al.*,¹ we could conclude that 74% of cancer patients with a tunnelled indwelling intrathecal catheter reported their satisfaction as either good or excellent. Only 26% of the patients were poorly or fairly pleased with an intrathecal catheter.

A simple, nonimplanted system in debilitated patients late in the course of their disease seems to be both easier to place and easier to use at home.²⁷ Implantation of an external, tunnelled intrathecal catheter is quick and easy to perform in the majority of cases and is less invasive than the implantation of a subcutaneous pump.²⁷ Despite the ease and minimal invasiveness of implanting an external, tunnelled intrathecal catheter, there is a certain risk of serious complications.²⁵ The clinical decision to implant an intrathecal catheter, however, is influenced by the predicted benefit *versus* the risk of complications. To our knowledge, there are still no robust estimates or meta-analyses for serious complications such as infection, neurologic injury, bleeding, or death due to an external intrathecal catheter.

Infection

We found an overall infection risk rate of 1.4% (95% CI, 0.5–3.8) for deep infections (one infection after 4,716 [95% CI, 1,613–13,699] catheter days), of 2.3% (95% CI, 0.8–6.1) for superficial infections (one infection after 3,247 [95% CI, 1,114–9,524] catheter days), and of 2.9% (95% CI, 1.1–7.4) for any catheter-related infections (one infection after 2,427 [95% CI, 831–7,092] catheter days). Therefore, every 71st patient had a deep infection after an average of 54 catheter days. Unfortunately, only one article²¹ indicated that the deep infection case described in the article occurred after 145 catheter days, and the superficial infection case occurred after 130 catheter days. Of the other articles, we are unaware of the time at which infections occurred.

These risks seem to be quite low and comparable to the infection rates reported for chronic indwelling epidural catheters (1.2% for deep infection, 4.6% for superficial infections, and 6.1% for any catheter-related infection).⁶ In patients with subcutaneously implanted ports, Holmfred *et al.*⁸ found a rate of 2% (95% CI, 0–5.8) for deep infection and a rate of 6% (95% CI, 0–12.6) for superficial infections. These infection rates are even higher than the rates in our analysis. However, the study by Holmfred *et al.* was conducted prospectively, whereas in our analysis only approximately half of the included patients were studied in a prospective manner.

A recent overview by Follett *et al.*,²⁸ with a total of 700 mainly noncancer pain patients, found an implanted drug-delivery system infection rate of one infection every 7,620 device months. Combining all studies, 36 infections involving 35 separate patients were reported in a total of 700 patients (5% overall infection rate). The majority (57–80%) of infections in each study involved the pump pocket site. The aggregate proportion of cases that were treated with complete or partial device removal also varied from 57% to 80%. All of the patients experienced resolution of their infections by the time each study or observation period had ended. No deaths or episodes of drug withdrawal were reported.

Patients with implanted pump systems had fewer deep infections per time unit (one deep infection in 127 months in our study *vs.* one deep infection in 7,620 months).²⁸ However, the individual risk of developing a deep infection was 1.4% in our study *versus* as much as 5% in the Follett study, although patient condition in cancer patients is probably much more serious than in a patient population with predominantly noncancer pain. This divergence is well explained by differences in the duration of application. Cancer patients in our study had an external catheter for an average of 55 days, whereas implanted pump patients in the Follett study had their device for several months (mean follow-up varied from 6.4 to 14.1 months). Nevertheless, the individual risk of developing a deep infection with external pumps in our

study was lower than in the Follett study with implanted pumps.

Unfortunately, in our study it was not possible to identify clear risk factors for infections. Furthermore, it remains unclear whether different implantation techniques influenced the frequency of infections. Nitescu *et al.*²⁰ found microbial contamination in approximately 20% of cultures from cassettes, syringes, and filters; however, no patients developed symptoms of meningeal infection. The catheter hub is believed to be the most important point of entry for microbes.²⁹ When bacterial filters are perfused with reduced volumes and at low injection pressures, the filters maintain sufficient antimicrobial function for more than 60 days.²⁹ Therefore, it does not seem unreasonable to change bacterial filters only every 60 days. In addition, some authors advocate the administration of prophylactic antibiotics through the intrathecal catheter.³⁰ In case of infected catheters, it also seems reasonable to consider not removing the catheter, especially in case of an epidural catheter.²⁵ One prospective article⁸ reporting on patients with implanted subcutaneous ports found no difference in infection rate when perfusing prophylactic antibiotics. In our analysis, it remains unclear how the prophylactic use of antibiotics influences the rate of infection. It is in addition unclear how often syringes, cassettes, and filters were changed. This could be an important factor influencing the rate of infections.

An epidural catheter has the (theoretical) advantage of having the dura as a natural barrier preventing the spread of an infection to the spinal cord. On the other hand, there are data reporting similar infection rates with intrathecal and epidural administration.²¹ Furthermore, the epidural route is not recommended for long-term use, because of increasing technical problems associated with epidural fibrosis.^{15,31,32}

Bleeding and Neurologic Injury

A 0.9% risk of bleeding or even the development of an intrathecal or epidural hematoma with devastating neurologic sequelae seems to be less of a problem, although cancer patients have many factors contributing to the likelihood of a coagulation disorder. Surprisingly, we could not identify clear reports on new neurologic injuries after introducing an intrathecal catheter. Only two cases with spinal cord compression were described. However, the reasons for this finding were not clear (bleeding or metastasis). All other cases reporting neurologic injuries involved patients with previous neurologic findings and injuries before inserting the indwelling intrathecal catheter. The assumption that intraspinal cannulation is contraindicated in all patients with known vertebral metastatic lesions is not supported in clinical practice.¹³

Granuloma

In our survey, we found no information on catheter-associated granulomas. However, there are several studies and case reports^{33,34} describing neurologic problems due to granulomas, especially in noncancer patients with implanted long-term intrathecal catheters. Several explanations are possible: (1) too short a duration of catheter placement to develop a clinically relevant granuloma, (2) lack of prospective and well-designed studies, (3) underreporting because of fear of legal action, and (4) “non-detection” of a catheter-associated death or granulomas in the context of a severe malignant illness with lethal exit.

Another important issue could be the concentrations of opioids applied. Unfortunately, it was not possible to identify the concentrations of opioids in the articles investigated. Nevertheless, we found a dose range of 2.3–11 mg morphine per day. An overview by Miele *et al.*³⁴ reported similar daily doses with exception of one article with excessive daily doses (110 mg morphine per day). Perhaps one of the best explanations for not finding granulomas is the small patient number. Although accepting the general reported incidence of approximately 1%,³⁴ we should have detected a few cases from a statistical point of view.

In a postmortem pathoanatomical examination,¹² granulomas were found in 2 of 15 patients (risk, 13%; 95% CI, 0–31). These patients had no new neurologic symptoms after insertion of an intrathecal catheter. Therefore, the development of catheter-associated granulomas is not likely to have impaired the neurologic situation of the patients.

Deaths

No reports of catheter-related death were found. However, there were few reports on respiratory depression and even arrest. Because it was not our intention to identify respiratory problems, our results regarding respiratory complications are doubtful. Nevertheless, we found an incidence of three respiratory arrests and two respiratory depressions in 247 patients. These figures seem to be high; however, most could be attributed to handling errors. Further studies are mandatory to determine the risk of respiratory depression.

Implanted versus External

There is some debate about the technique appropriate for implanting a chronic indwelling intrathecal catheter. Some authors advocate implanting a pump to prevent infection-related complications. If life expectancy is longer than 3–6 months, such an implanted system may be more convenient.⁴ Furthermore, the use of externalized tunnelled intrathecal catheters has not been associated with higher rates of complications.²⁵ We think that patients with implanted pumps require full-time assis-

tance with specialized and advanced levels of knowledge, which often cannot be guaranteed. Because our chronic pain division cannot provide such support, we do not implant pumps. In addition, the handling of implanted pumps requires specialized knowledge and training in the programming and refilling of a pump. In addition, every anesthetist on call should be able to handle an external implanted catheter.

Last but not least, a simple nonimplanted system in debilitated patients late in the course of their disease seems to be both easier to place and easier to use at home.²⁷

One of the limitations of our analysis is its retrospective nature, a problem encountered whenever conducting a meta-analysis regarding rare complications. Only 30% of the studies included were prospective, 40% were retrospective, and 30% were of unknown nature. Another recent published analysis⁶ on a similar topic identified eight retrospective and only four prospective studies. Therefore, it seems that the amount of identified retrospective studies is quite high for this type of analysis.

A further limitation is the fairly small number of identified articles with relatively few patients. In addition, the inclusion criteria of a case threshold of 20 is arbitrary. The caseload is certainly higher in larger case series. We suppose that centers with higher caseloads have more standardized procedures for implantation and more experience. Such data are, therefore, more homogenous and likewise more comparable. Furthermore, the accuracy of statistical statements in larger case series is higher than in small series.

A third limitation of our study is the possibility of different definitions classifying infections and bleeding between the included articles. In particular, the definition for superficial infection could be quite different between the included studies: Is redness of the catheter exit enough for a superficial infection, or is a real superficial abscess mandatory? No clear definitions were provided in the included articles. Furthermore, we assume that deep infections have such a clinical impact and consequences that renders heterogeneity between studies less important. Therefore, it is likely that our analysis is more accurate regarding deep rather than superficial infections, because the identification of a deep infection is much more evident. Another source of inaccuracy could be underreporting due to concern of legal consequences.

Most of the studies did not report on detailed implantation technique or on the experience of the operator, both of which may contribute to the inhomogeneity of the included studies.

To obtain more detailed and accurate information, large and well-designed prospective studies are mandatory. Because most of the centers have a limited casel-

oad, it will be difficult for a center to obtain sufficiently large patient numbers.

Conclusion

Serious complications such as infection, bleeding, and neurologic injury in cancer patients with external chronic indwelling intrathecal catheters in the hospital and in the home setting are rare and of minor importance. The infection rates are comparable with other techniques, such as implanting subcutaneous ports. Considering that in a small number of cancer patients the only way to alleviate pain is to provide intrathecal medication, we think that weighing the benefits *versus* the risks leans more heavily toward the beneficial potential than toward the possibility of serious complications. We are convinced that an external intrathecal catheter can be a very good and cost-effective option to help this minority of patients. Special medical knowledge for physicians and education programs for patients and their relatives is mandatory.

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References

1. Kedlaya D, Reynolds L, Waldman S: Epidural and intrathecal analgesia for cancer pain. *Best Pract Res Clin Anaesthesiol* 2002; 16:651-65
2. Gerber H: The role of interventional pain therapy in palliative care [in German]. *Schweiz Rundsch Med Prax* 2004; 93:1240-6
3. Hassenbusch SJ, Paice JA, Patt RB, Bedder MD, Bell GK: Clinical realities and economic considerations: Economics of intrathecal therapy. *J Pain Symptom Manage* 1997; 14:S36-48
4. Bedder MD, Burchiel K, Larson A: Cost analysis of two implantable narcotic delivery systems. *J Pain Symptom Manage* 1991; 6:368-73
5. Nussbaum ES, Rigamonti D, Standiford H, Numaguchi Y, Wolf AL, Robinson WL: Spinal epidural abscess: A report of 40 cases and review. *Surg Neurol* 1992; 38:225-31
6. Ruppen W, Derry S, McQuay HJ, Moore RA: Infection rates associated with epidural indwelling catheters for seven days or longer: Systematic review and meta-analysis. *BMC Palliat Care* 2007; 6:3
7. Ruppen W, Derry S, McQuay H, Moore RA: Incidence of epidural hematoma, infection, and neurologic injury in obstetric patients with epidural analgesia/anesthesia. *ANESTHESIOLOGY* 2006; 105:394-9
8. Holmfred A, Vikerfors T, Berggren L, Gupta A: Intrathecal catheters with subcutaneous port systems in patients with severe cancer-related pain managed out of hospital: The risk of infection. *J Pain Symptom Manage* 2006; 31:568-72
9. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF: Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. *Quality of Reporting of Meta-analyses*. *Lancet* 1999; 354:1896-900
10. Team RDC: R: A Language and Environment for Statistical Computing. Vienna, Foundation for Statistical Computing, 2008
11. Wang JK: Intrathecal morphine for intractable pain secondary to cancer of pelvic organs. *Pain* 1985; 21:99-102
12. Sjöberg M, Karlsson PA, Nordborg C, Wallgren A, Nitescu P, Appelgren L, Linder LE, Cürelaru I: Neuropathologic findings after long-term intrathecal infusion of morphine and bupivacaine for pain treatment in cancer patients. *ANESTHESIOLOGY* 1992; 76:173-86
13. Du Pen S: Complications of neuraxial infusion in cancer patients. *Oncology (Williston Park)* 1999; 13:45-51

14. Nitescu P, Dahm P, Appelgren L, Cürelaru I: Continuous infusion of opioid and bupivacaine by externalized intrathecal catheters in long-term treatment of "refractory" nonmalignant pain. *Clin J Pain* 1998; 14:17-28
15. Crul BJ, Delhaas EM: Technical complications during long-term subarachnoid or epidural administration of morphine in terminally ill cancer patients: A review of 140 cases. *Reg Anesth* 1991; 16:209-13
16. Van Dongen RT, Crul BJ, De Bock M: Long-term intrathecal infusion of morphine *via* the intrathecal route [in French]. *Cah Anesthesiol* 1985; 33:47-9
17. Gestin Y, Pere N, Solassol C, Stapf P: Prolonged administration of morphine *via* the intrathecal route [in French]. *Ann Fr Anesth Reanim* 1986; 5:346-50
18. Gestin Y, Pere N, Solassol C: Long-term intrathecal isobaric morphine therapy [in French]. *Ann Fr Anesth Reanim* 1986; 5:346-50
19. Nitescu P, Appelgren L, Hultman E, Linder LE, Sjöberg M, Cürelaru I: Long-term, open catheterization of the spinal subarachnoid space for continuous infusion of narcotic and bupivacaine in patients with "refractory" cancer pain: A technique of catheterization and its problems and complications. *Clin J Pain* 1991; 7:143-61
20. Nitescu P, Hultman E, Appelgren L, Linder LE, Cürelaru I: Bacteriology, drug stability and exchange of percutaneous delivery systems and antibacterial filters in long-term intrathecal infusion of opioid drugs and bupivacaine in "refractory" pain. *Clin J Pain* 1992; 8:324-37
21. Nitescu P, Sjöberg M, Appelgren L, Cürelaru I: Complications of intrathecal opioids and bupivacaine in the treatment of "refractory" cancer pain. *Clin J Pain* 1995; 11:45-62
22. Baker L, Lee M, Regnard C, Crack L, Callin S: Evolving spinal analgesia practice in palliative care. *Palliat Med* 2004; 18:507-15
23. Devulder J, Ghys L, Dhondt W, Rolly G: Spinal analgesia in terminal care: Risk *versus* benefit. *J Pain Symptom Manage* 1994; 9:75-81
24. Gestin Y, Vainio A, Pegurier AM: Long-term intrathecal infusion of morphine in the home care of patients with advanced cancer. *Acta Anaesthesiol Scand* 1997; 41:12-7
25. Mercadante S: Neuraxial techniques for cancer pain: An opinion about unresolved therapeutic dilemmas. *Reg Anesth Pain Med* 1999; 24:74-83
26. Krames ES: Intrathecal infusional therapies for intractable pain: Patient management guidelines. *J Pain Symptom Manage* 1993; 8:36-46
27. Mercadante S: Intrathecal morphine and bupivacaine in advanced cancer pain patients implanted at home. *J Pain Symptom Manage* 1994; 9:201-7
28. Follett KA, Boortz-Marx RL, Drake JM, DuPen S, Schneider SJ, Turner MS, Coffey RJ: Prevention and management of intrathecal drug delivery and spinal cord stimulation system infections. *ANESTHESIOLOGY* 2004; 100:1582-94
29. De Cicco M, Matovic M, Castellani GT, Basaglia G, Santini G, Del Pup C, Fantin D, Testa V: Time-dependent efficacy of bacterial filters and infection risk in long-term epidural catheterization. *ANESTHESIOLOGY* 1995; 82:765-71
30. Mercadante S, Serretta R, Sapio M, Villari P, Calderone L: When all else fails: Stepwise multiple solutions for a complex cancer pain syndrome. *Support Care Cancer* 1999; 7:47-50
31. Hogan Q, Haddox JD, Abram S, Weissman D, Taylor ML, Janjan N: Epidural opiates and local anesthetics for the management of cancer pain. *Pain* 1991; 46:271-9
32. Erdine S, Aldemir T: Long-term results of peridural morphine in 225 patients. *Pain* 1991; 45:155-9
33. Miele VJ, Price K, Bloomfield S, Hogg J, Bailes J: Intrathecal morphine therapy related granulomas: Two case reports. *W V Med J* 2006; 102:16-8
34. Miele VJ, Price KO, Bloomfield S, Hogg J, Bailes JE: A review of intrathecal morphine therapy related granulomas. *Eur J Pain* 2006; 10:251-61

Appendix: Search Strategy for PubMed

Medical subject heading (MeSH) term search for PubMed:

1. Search "Anesthesia, spinal"[MeSH]
2. Search "Anesthesia, intrathecal"[MeSH]
3. Search "Anesthesia, intraspinal"[MeSH]
4. Search "Analgesia, spinal"[MeSH]
5. Search "Spinal puncture"[MeSH]
6. Search "Injections, spinal"[MeSH]
7. Search "Spinal catheter"[MeSH]
8. Search "Myelography"[MeSH]
9. Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. Search (spin* or intraspinal or dura* or intradural or intrathecal* or theca* or subarachnoid*) near (puncture* or inject* or anesth* or anaesth or needle*)
11. Search #9 OR #10
12. "Spinal cord injuries"[MeSH]
13. Search (nerv* NEAR injury) OR (nerv* NEAR damage*)

14. Search #12 OR #13
15. Search "Spinal abscess"[MeSH] (epidural abscess, spinal)
16. Search (abscess* OR infection*) AND (spinal* OR intrathecal* OR intraspinal*)
17. Search #15 OR #16
18. Search "Hematoma"[MeSH]
19. Search bleed* OR hemat* OR haemat*
20. Search #18 OR #19
21. Search "Granuloma"[MeSH]
22. Search "Granulom*"
23. Search #21 OR #22
24. Search #14 OR #17 OR #20 OR #23
25. Search #11 AND #24

Full text search for PubMed: ((Granulom*) OR (bleed* OR hemat* OR haemat*) OR ("Hematoma"[MeSH] OR "Hematoma, Subdural, Spinal"[MeSH] OR "Hematoma, Subdural"[MeSH] OR "Hematoma, Epidural, Spinal"[MeSH]) OR (Hematoma) OR ((abscess* OR infection*) AND (spinal* OR intrathecal* OR intraspinal*)) OR ("Spinal Cord Injuries"[MeSH] AND "Spinal Cord Injuries"[MeSH])) AND ((("Anesthesia, Spinal"[MeSH] OR "Spinal Puncture"[MeSH] OR "Injections, Spinal"[MeSH] OR "Myelography"[MeSH]) OR ((spin* OR intraspinal OR dura* OR intradural OR intrathecal* OR theca* OR subarachnoid*) AND near AND (puncture* OR inject* OR anesth* OR anaesth OR needle*))))).

The search strategies for MEDLINE and EMBASE were performed in a similar way.