Retrospective Study

Catheter-tip Granulomas Associated with Intrathecal Drug Delivery – A Two-Center Experience Identifying 13 Cases

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Background: Intrathecal (IT) drug therapy with implanted pumps is an effective treatment modality for chronic pain and/or spasticity, especially after non-invasive treatment has failed. Long-term use of intrathecal opioids may cause formation of inflammatory masses at the tip of intrathecal catheters, possibly leading to neurological deficits and/or catheter revision.

Objective: We aimed to identify risk factors for catheter-tip granuloma (CG) formation.

Study Design: Retrospective study.

Setting: Tertiary Spine Centers in Germany and Switzerland

Methods: We retrospectively reviewed data at 2 Swiss centers (Kantonsspital St. Gallen, Swiss Paraplegic Centre Nottwil) between 01/1994 and 10/2013. Collected data were age at operation, gender, smoking status, previous spinal operations, spinal level of catheter-tip, clinical symptoms, catheter testing with contrast agent, applied drugs, drug concentration, as well as cumulative daily drug dosages.

Results: Thirteen patients with a mean age of 52.6 years and CG formation after a mean of 6.9 years of follow-up were identified and compared to 54 patients of similar age and length of follow-up (48.6 years, $P = 0.535$; follow-up 5.3 years, $P = 0.236$) without CG. In the analysis of risk factors, catheter ending in the middle thoracic spine (Th4-8; 38.5 vs. 6.5%; $P = 0.010$), previous spinal surgery (75 vs. 41%; $P = 0.051$), and chronic pain as an underlying primary symptom for IT drug therapy (100 vs. 56%, $P = 0.003$) were associated with CG formation. IT drug therapy for spasticity appeared to be much less associated with CG formation (0 vs. 44%, $P = .0003$). As the symptomatology is closely related to the medical treatment applied, patients with CG were more likely to be treated with IT morphine (77 vs. 20%; $P < 0.001$), and as tendency with IT clonidine (54 vs. 26%; $P = 0.092$) and IT bupivacaine (46 vs. 20%; $P = 0.077$). Average in-pump morphine concentration (30.3 vs. 19.5 mg/mL; $P = 0.05$) as well as average daily dose of morphine (12.5 vs. 6.2 mg/d; $P = 0.037$) were significantly higher in the CG group. Smoking could not be identified as risk factor for CG formation.

Limitations: Limitations include the retrospective approach, the limited group size of granuloma patients, as well as missing data in the investigated patient groups.

Conclusion: Our patient cohort with CG differed in some features, of which some like catheter localization, choice, dosage, and the concentration of drugs are potentially modifiable. These results could contribute to the prevention of CG in the future.

Key words: Intrathecal drug delivery, intrathecal cathether-tip granuloma, intrathecal cathether-tip inflammatory masses, intrathecal morphine, drug pump complications

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Intrathecal (IT) drug therapy with implanted pumps is considered as an effective treatment modality for patients suffering from chronic pain and/or spasticity (1). As recommended in the Polyanalgetic Consensus Conference 2012, the indication for IT drug therapy has to be indexed by a multidisciplinary team (2). Especially after non-invasive treatment has failed, IT drug delivery represents a generally safe and effective option for chronic pain management, with success rates of 61% to 75% reported in recent series (3,4). Even though uncommon, acute, subacute, and long-term side effects can appear, including neural damage, intraspinal hemorrhage during and after placement of IT-catheter insertion (hemorrhage less common in the abdominal pouch), infection and wound-healing difficulties in the subacute phase as well as erectile dysfunction (5), material (catheter/pump) dysfunction, and end-of-life battery issues. As a further and generally rare complication, the formation of catheter-tip granulomas (CG; other terminology: inflammatory masses) has been increasingly reported (6). Still, the currently available literature is scarce regarding the identification of risk factors for CG after IT therapy, so far only encompassing case reports and one retrospective study on 4 patients with CG (7-9).

As we have encountered CG increasingly during the last years, we have undertaken the effort to collect the cases of CG formation that were treated by our department. The aim of this study was to search and identify possible risk factors of CG formation (10), as there is great need for this information when consulting with our patients.

Methods

Patients

We retrospectively reviewed all charts of patients who received IT infusion therapy with an implanted pump between 01/1994 and 10/2013. The data was collected at 2 Swiss centers: the Department of Neurosurgery, Kantonsspital St. Gallen (KSSG) and the Swiss Paraplegic Centre in Nottwil (SPZ). Thirteen patients with CG were identified; 54 patients of similar age, gender, and length of follow-up without evidence of CG served as controls. All diagnoses of CG were confirmed by spinal magnetic resonance imaging (MRI). All patients gave informed consent.

Collected Data

Collected data included age at first surgery for pump implantation, gender, smoking status (smoker, ex-smoker, never-smoker), and previous surgery of the spine (including stabilization after trauma and surgery for degenerative spine disease). The spinal level of the catheter tip was determined in every patient on available imaging studies, and was grouped to the cervical spine, upper thoracic spine (Th1-4), middle thoracic spine (Th5-8), lower thoracic spine (Th9-12), upper lumbar spine (L1-3), and lower lumbar spine (L4-5). In the group of patients with CG, the time interval from initial implantation of the pump until CG detection on imaging studies was determined. In the control group, the total time of implanted IT catheter with drug application was determined as time from initial implantation of the pump until end of follow-up (this includes end of therapy, explantation of the system, or the time point data was collected). Concerning the indication for IT therapy, the leading presenting symptom was identified based on the patient chart before initial implantation of the pump. Here, we divided intractable pain (e.g., after trauma, failed back surgery syndrome) from spasticity (e.g., cerebral palsy, multiple sclerosis). Catheter testing with contrast agent is used in our department for examination of catheter system functionality. As we noticed a coincidence of catheter testing with CG formation, for this study purpose, frequency of testing (before CG diagnosis) was recorded.

As our department follows all patients after implantation of an IT pump, we could analyze applied drugs that were administered to the patient at any time point since the index surgery; for study purposes, however, we recorded only substances that had been applied for at least 12 weeks. Similarly, every adjustment of the drug concentration inside the pump, as well as the cumulative IT daily dosages for each drug was recorded.

Statistics

Statistical analysis was performed using the Fisher's exact test, the two-tailed Mann–Whitney-test, or the Wilcoxon Signed Ranks Test as appropriate. All calculations were made with SPSS 22.0 software for Windows (IBM, Armonk, USA). Statistical significance was declared if P-value was ≤ 0.05.

Results

Patient Population

Between 01/1994 and 10/2013, a total of 108 and 96 patients underwent surgery for IT drug therapy

at KSSG and SPZ, respectively. One hundred fifty-nine (77.9%) of the patients were available for follow-up. Thirteen of 159 patients, according to a prevalence of 8.2%, developed a CG (proven by MRI [11]) during the follow-up and were included in this study. We matched the study group with 54 control patients that were chosen randomly from our cohort to enhance the statistical power (Fig. 1). Table 1 describes basic characteristics of the study and control group, not differing in basic characteristics such as age or gender.

Examined Assumed Risk Factors

Catheter Tip Location

Exact catheter tip location could be determined in all study patients and 85.2% of the control group. The location of the catheter tip in the spine differed somewhat between the patients with and without CG (Table 2). We found a predominance for CG in the middle thoracic spine (38.5 vs. 6.5%; $P = 0.010$) while no CG was found in the lumbar (0 vs. 17.4%; $P = 0.179$) or cervical spine (0 vs. 2.2%; $P = 1.000$).

Previous Spinal Surgery

Details on previous spine surgery could be obtained in 12 patients with CG (92.3%) and 42 of the control group (77.8%). Seventy-five percent of the patients with CG compared to 40.5% of the control group had a history of previous spine surgery for degenerative or traumatic spine disease before implantation of the IT catheter ($P = 0.051$; Table 2).

Smoking Status

Of 9 patients with a CG (69.2%) and 31 of the control group (57.4%), the smoking status could be determined. Eleven point one percent of the patients who developed a CG were smokers at the time of pump insertion, 33.3% of these patients were former smokers, and 55.6% of patients never smoked as compared to 19.4%, 12.9%, and 67.7% of the control group. No difference was found between the study patients and control group concerning the smoking status (Table 2). Also when current and former smoking status were combined for analysis, we found no impact of smoking status on CG formation (44.4% vs. 32.3%; $P = 0.693$).

Total Time of Intrathecal Implanted Catheter with Drug Application

The average total time interval of implanted IT catheter was determined in all patients until granuloma formation detected by imaging studies in the CG group, as well as until last follow-up in the control group (Table 2). In the study group, CG was detected after a mean of 6.9 ± 4.7 years. In the control group, total average time interval of implanted catheters was a little shorter with 5.3 ± 3.9 years, however statistically insignificant ($P = 0.236$).

Catheter Testing with Contrast Agent

As invasive testing of the functionality of the cath-

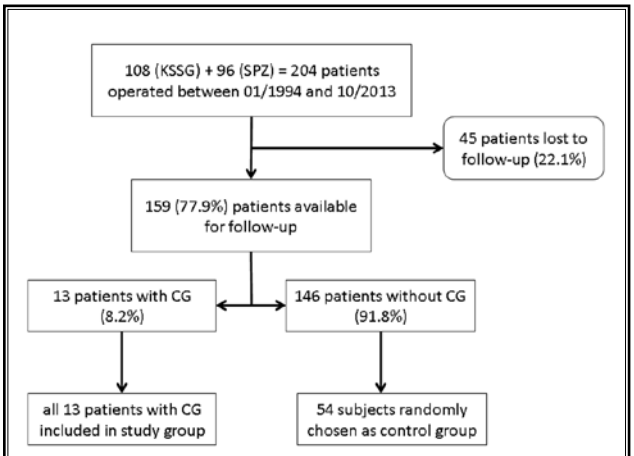

Fig. 1. *From a total of 159 patients operated on between 01/1994 and 10/2013 at the Kantonsspital St. Gallen (KSSG) and Schweizer Paraplegikerzentrum Nottwil (SPZ) with available follow-up data, a catheter-tip granuloma (CG) was detected in 13 (8.2%) patients.*

Table 1. *Characteristics of patients with CG as well as control patients with intrathecal drug therapy following pump implantation.*

	Control group	Granuloma group	*P* -Value
Total number of patients	54	13	
Age at index surgery (in years; mean ± SD)	48.6 ± 17.5	52.6 ± 9.2	0.535
Gender			
Male	24 (44.4%)	5 (38.5%)	0.765
Female	30 (55.6%)	8 (61.5%)	

Table 2. *Examined risk factors for granuloma development in CG patients as well as in control patients.*

	Control group	Granuloma group	*P*-Value
Applied drugs			
Total number of patients	54	13	
Fentanyl	3 (6%)	2 (15%)	0.247
Morphine	11 (20%)	10 (77%)	<0.001
Hydromorphone	11 (20%)	3 (23%)	1,000
Clonidine	14 (26%)	7 (54%)	0.092
Bupivacaine	11 (20%)	6 (46%)	0.077
Baclofen	25 (46%)	2 (15%)	0.059
Ziconitide	3 (6%)	2 (15%)	0.247
Leading clinical symptom			
Total number of patients	54	13	
Pain	30 (56%)	13 (100%)	0.002
Spasticity	24 (44%)	0 (0%)	0.003
Total time of intrathecal implanted catheter with drug application			
Total number of patients	54	13	
Time (years; mean ± SD)	5.3 ± 3.9	6.9 ± 4.7	0.236
Catheter tip location			
Total number of patients	46	13	
Cervical spine	1 (2.2%)	0 (0%)	1,000
Upper thoracic spine (Th1-Th4)	4 (8.7%)	1 (7.7%)	1,000
Middle thoracic spine (Th5-Th8)	3 (6.5%)	5 (38.5%)	0.010
Lower thoracic spine (Th9-Th12)	30 (65.2%)	7 (53.8%)	0.524
Upper lumbar spine (L1-L3)	4 (8.7%)	0 (0%)	0.566
Lower lumbar spine (L4-L5)	4 (8.7%)	0 (0%)	0.566
Previous spinal surgery			
Total number of patients	42	12	
Yes	17 (40.5%)	9 (75%)	0.051
No	25 (59.5%)	3 (35%)	
Smoking status			
Total number of patients	31	9	
Smokers	6 (19.4%)	1 (11.1%)	1,000
Ex-Smokers	4 (12.9%)	3 (33.3%)	0.316
Never-Smokers	21 (67.7%)	5 (55.6%)	0.693
Smokers and Ex-Smokers	10 (32.3%)	4 (44.4%)	0.693
Catheter testing with contrast agent			
Total number of patients	49	12	
Yes	20 (40.8%)	9 (75%)	0.052
No	29 (59.2%)	3 (25%)	

eter system by injecting contrast agent in the system might induce inflammation and thus impact granuloma formation, we analyzed previous catheter testing in 12 study patients (92.3%) and 49 of the control group with available data (90.7%; Table 2). Seventy-five percent of patients from the study group were subject to catheter testing with contrast agent before detection of the CG on subsequent imaging studies, while invasive testing was performed in 40.8% of the patients of the control group, indicating a statistical association ($P = 0.052$).

Leading Clinical Symptom, Indication for Surgery

Pain or spasticity as a leading clinical symptom could be determined from the files in all patients of the study and control groups (Table 2). Indication for IT pump implantation surgery was pain in 100% of the study patients as compared to 56% of the control group ($P = 0.002$). None of the patients with CG formation as compared to 44% of the control group suffered from spasticity as the leading clinical symptom ($P = 0.003$).

Applied Drugs, Concentration and Daily Dose of IT Morphine and Clonidine

The distribution of applied drugs differed strongly between the groups as is evident from Table 2. Table 3 outlines the drug and concentration used by the study patients at the time of granuloma formation. The use of IT morphine was highly associated with CG formation (77 vs. 20%, $P < 0.001$), while both bupivacaine ($P = 0.077$) and clonidine ($P = 0.092$) showed a tendency. Hydromorphone was used as single opioid in 23% of granuloma patients, and in 20% of controls ($P = 1.000$). In contrast, baclofen showed a reversed association with CG formation by trend ($P = 0.059$). The other and less frequently applied substances such as fentanyl and ziconotide did not reveal a correlation to CG formation (Table 2).

As the effect of morphine on CG formation was obvious by our data, we additionally looked at the in-pump morphine concentration and calculated the total daily dose of morphine application by the IT pump system (Table 4, Fig. 2). Data were available for 11 patients in the study group and 8 patients in the control group receiving IT morphine. The average concentration of in-pump morphine was 30.3 ± 5.0 mg/mL for the study group as compared to 19.5 ± 5.9 mg/mL in the control group, the difference reaching statistical significance ($P = 0.050$). A daily dose of 12.5 ± 5.6 mg of IT morphine on average was applied to patients experiencing CG formation. This dose was significantly lower in the control group, receiving 6.2 ± 2.6 mg morphine per day ($P = 0.037$).

Clonidine was applied more often in the granuloma group (54 vs. 26%, $P = 0.092$), and also average in-pump concentration of clonidine differed between both groups, but was not statistically significant (960.9 vs. 234.4 µg/mL, $P = 0.753$), and there was no statistical difference between average daily doses of applied clonidine (Table 4).

Discussion

Analyzing the so-far largest published series of 13 patients with CG as a delayed complication following IT drug therapy with implanted pumps, we found pain as the leading symptom, and confirmed morphine as the pharmacological agent, as well as higher morphine dosage and concentration to be highly associated with CG formation. CG formation was furthermore shown to correlate with catheter-tip placement in the middle thoracic spine (Th5-8), previous spinal surgery, and invasive catheter testing by injecting contrast agent, while our data did not support smoking or length of IT therapy as risk factors.

Definition and Prevalence

The first description of a CG was reported in 1991 by North et al (12). Histopathologically, CG are aseptic inflammatory masses consisting of inflammatory cells like macrophages, eosinophils, and lymphocytes (13) that may originate from the arachnoid layer (14). As a critical component of CG formation, an inflammatory process including the migration and activation of mast cells has been proposed (13). Interestingly, an inhibitor of mast cell degranulation prevented CG formation after high dose IT morphine therapy in an animal study (15), thus underlying the pathophysiological model.

The prevalence of CG in patients with IT drug therapy was estimated as 3% in one imaging study of 208 patients (16), compared to a higher rate of 8.2% revealed in our study.

Management of CG

Typically, CG present with signs of pump malfunction (persistent pain despite increased opioid dosages leading to insufficient pain management or even signs and symptoms of drug deprivation), as they obstruct the lumen of the drug application catheter. While CG themselves can lead to (radicular) pain and even neurological deficits by compressing the spinal cord or exiting nerve roots, they may also be asymptomatic

Table 3. *Characteristics of granuloma patients at the time at granuloma detection. x = missing data*

Patient number	Age	Gender	Catheter level	Used drugs	Total infusion time [d]	Drug concentration [mg/mL]	Drug dosage [mg/day]
1	59	male	Th4/5	Hydromorphone Ziconitide	6881 267	10.0 0.003	5.7 0.0022
2	56	female	Th7	Morphine	3586	40.0	15.98
3	72	male	Th10	Morphine Bupivacaine Baclofen Clonidine	x x x x	x x 0.1 x	x x 0.0899 x
4	59	female	Th6/7	Hydromorphone	650	10.0	4.8
4	68	female	Th6	Ziconitide	2979	0.0125	0.0131
5	63	male	Th11/12	Morphine Baclofen	3727 3337	28.9 0.556	21.1 0.406
6	59	female	Th6/7	Morphine Clonidine	1388 1388	45.0 0.45	32.9 0.33
7	56	female	Th11	Morphine Clonidine	2506 2506	34.5 0.525	13.35 0.157
8	35	female	Th3/4	Morphine Clonidine	918 918	45.0 0.2	38.0 0.127
9	57	female	Th10/11	Morphine Clonidine	1697 1697	20.0 0.1	7.2 0.044
9	58	female	Th10/11	Morphine Clonidine	60 x	20.0 x	1.5 x
10	59	male	Th9/10	Morphine Clonidine	670 670	36.0 0.4	20.0 x
11	66	female	Th8/9	Morphine Clonidine Bupivacaine	4640 4640 4640	16.0 0.125 12.5	6.0 0.468 4.68
12	46	female	Th10	Morphine Clonidine Bupivacaine	2293 2293 x	10.0 0.2 10.0	1.9 0.388 1.94
13	66	male	Th10	Hydromorphone Bupivacaine Ziconitide	2368 764 325	4 22.0 0.002	30.9 17.0 0.0017

(17). Generally, diagnosis is validated by MRI preferably with contrast agent (7). In addition, histopathological confirmation can be performed. In case of CG in patients under IT opioid delivery, termination of IT drug application may lead to shrinkage of the CG (18) and render more invasive treatment unnecessary. However, it should be emphasized that adequate oral or intravenous substitution of usually high equivalence dosages of opioids must be facilitated. Depending on the daily morphine dose administered at our department we prefer inpatient care for at least 2 – 3 days until a stable situation has been reached. In case of neurological deterioration due to mass effect of the CG or impossibility of oral substitution, treatment options include resection of the mass (19) and catheter ligation leaving the CG in situ, with or without implantation of a new catheter system.

Risk Factors for CG Formation

Morphine and Other Opioids

So far, the literature concerning risk factors for CG formation is limited and comprises case reports (20), literature reviews (21,22), and small (8,17) and larger series reports without control groups only (23). However, it is generally assumed that CG are associated with use of IT opioids or opioid drug combinations, which is strongly supported by our own findings demonstrating a coincidence of CG-formation with opioid derivates in each but one case. In our series, morphine was the drug

Table 4. Analysis of morphin concentration inside the pump as well as daily dose of intrathecal morphine in patients with and without CG.

	Control group	Granuloma group	*P*-Value
Total number of patients	11	8	
Morphine concentration inside the pump (in mg/ml; mean ± SD)	19.5 ± 5.9	30.3 ± 5.0	0.050
Total number of patients	11	8	
Daily dose of intrathecal morphine (in mg/d; mean ± SD)	6.2 ± 2.6	12.5 ± 5.6	0.037
Total number of patients	10	6	
Clonidine concentration inside the pump (in µg/ml; mean ± SD)	234.4 ± 96.3	960.9 ± 144.7	0.753
Total number of patients	10	6	
Daily dose of intrathecal clonidine (in µg/d; mean ± SD)	870.3 ± 647.2	876.9 ± 36.2	0.116

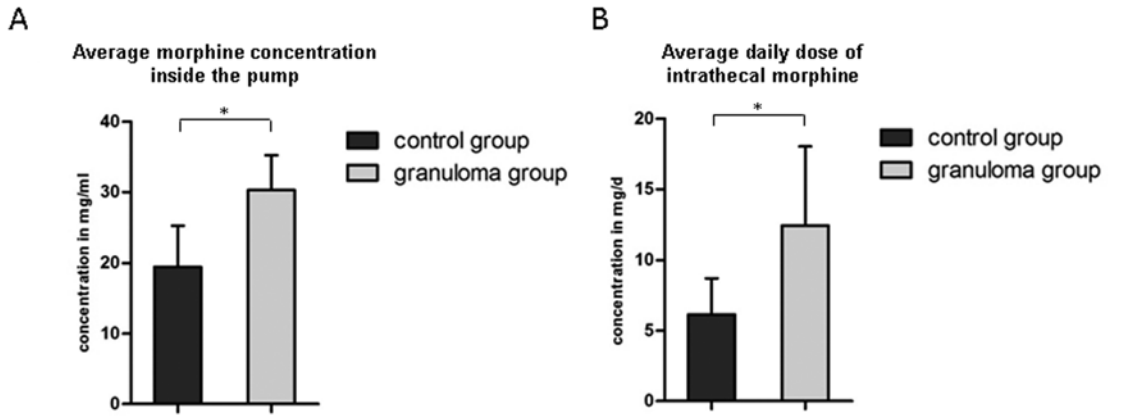

Fig. 2. *Average concentration of morphine inside the pump in the control group and in the granuloma group (A). The average daily dose of IT morphine in controls and in the granuloma group is shown in (B).*

strongest associated with CG-formation. A significant effect, however, was not evident for other opioid derivatives such as fentanyl and hydromorphone, that have – however – also been related to CG formation before (24,25). Taking into consideration the very limited number of patients analyzed here as a clear limitation, our results may still indicate that activation of the opioid receptors could play a major role in the pathophysiology of CG formation.

In preclinical studies, higher IT morphine doses caused a higher incidence of CG formation, which is in line with previous clinical reports (13,14,26,27). Likewise, our own data clearly demonstrate that especially patients with higher morphine doses are at risk to develop CG. In fact, the average daily dose of IT morphine was twice as high in the group of patients with a granuloma as compared to the control group. A similar effect was evident for the average concentration of administered morphine, which was significantly higher in the granuloma group (Table 4).

Non-opioid Pharmacological Agents

Clonidine as an alpha-2 receptor antagonist may be used "off label" in carefully selected patients if pain is not sufficiently responsive to opioid application. Due to its agonist effect, it helps to avoid morphine dose escalation and sometimes allows the reduction of daily morphine doses (28). As such, the use of clonidine to prevent CG formation has been discussed before (7,14,29). Our results demonstrate that 54% of patients with CG were treated with clonidine at the time of CG diagnosis as compared to only 26% of the control group (P = 0.092). In our granuloma group, only 2 patients received morphine without clonidine, compared to 9 patients treated with morphine combined with clonidine (Table 3), with comparable mean daily morphine doses (18.5 mg/mL and 15.1 mg/mL, respectively). Therefore, neither a protective nor a harmful effect of clonidine

could be revealed, mainly due to the small subgroups and to the "routinely" administration of clonidine.

Also IT baclofen as single agent has been associated with CG formation in previous reports (30-32). While our current series also includes 2 patients with CG formation under baclofen, this drug seems to be much less predisposing for CG formation than opioids (Table 2). Of note, we report a patient with a second CG formation under ziconotide as monotherapy, after the patient developed a granuloma under hydromorphone monotherapy several months before, which has so far not been reported in the literature (Table 3).

Timing of CG Formation

CG typically appear after long-term use of IT drug application (6), and also in our series the average delay between IT pump insertion and diagnosis of the CG was > 6 years (Table 2). Notwithstanding their slow onset in most of cases, CG still seem to be capable of rapid and dynamic growth, and CG formation has been reported after only 5 weeks of IT morphine administration (18) as well as with reoccurrence within an interval of only a few weeks (33,34). When compared to the control group, we found no difference in the duration of treatment until CG-formation, indicating that length of IT drug treatment itself is no risk factor.

Location of the Catheter-tip

Up to now, there is no scientific evidence of a relationship between the catheter-tip position and CG development (6). Interestingly, CG formation was more frequent in our series when catheter-tips ended in the middle thoracic spine (Th5-8). From Table 3 it is evident that this effect was not confounded by differential drug application. We observed no cases with CG formation for either the cervical or lumbar spine region. A feasible reason for that could be the lower cerebrospinal fluid flow velocity in the thoracal region compared to the lumbar region (35). As the level of the catheter-tip might play a role for CG development, we recommend placing the catheter-tip in the lower thoracic or thoraco-lumbar spine, if feasible.

Previous Spine Surgery

Spine surgery may induce transitory or chronic inflammation affecting the epidural space as well as the intradural portions of the nervous system. As such it was suggested that this could be a risk factor for CG formation (36). Our data indicates that 75% of patients with a CG had undergone some type of spine surgery before catheter insertion, while this was less often the case in the control group (40.5%; $P = 0.051$). Besides induction of intraspinal chronic inflammation, a further reason could be modified spinal canal anatomy with altered cerebrospinal fluid dynamics.

Smoking Status

Smoking is well known for its multiple negative effects on bodily health, also including the structures of the spine (37). Our analysis, unfortunately comprising only a subset of patients with available data, could not identify smoking status as a risk factor for CG development (Table 2).

Invasive Catheter Testing

If a patient's therapy fails with drug resistance or worsened symptoms, catheter testing with contrast agent is performed in our department. In the recent years we had the clinical suspicion that invasive catheter testing was associated with CG development. Our data indicate a correlation of invasive catheter testing with CG formation by trend (Table 2). Catheter testing was usually performed in coincidence with ineffectiveness of pain therapy, many weeks as well as some days before the diagnosis of CG was established; still, this observed association does not allow any causal conclusion. The observed association might rather be confounded as patients with CG and pump dysfunction were more likely to be tested than patients without CG. Nevertheless, successful catheter testing could not exclude a growing granuloma, but possibly accelerating inflammatory processes and granuloma growth. Still, an influence of the contrast agent on CG cannot be excluded by our results and should be evaluated in further research.

Conclusions

We found pain, morphine use, as well as higher morphine dosage and concentration to be highly associated with CG formation. It was furthermore shown to correlate with catheter-tip placement in the middle thoracic spine (Th5-8), previous spinal surgery, and invasive catheter testing by injecting contrast agent, while our data did not support smoking or length of IT therapy as risk factors. Taking this into consideration, we recommend diluting the morphine concentration and placing the catheter tip lower than the middle thoracic region whenever possible. Physicians should be more suspicious of CG in patients with previous spinal surgery and in whom catheter testing with contrast agent was recently performed.

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