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Intrathecal granuloma formation as result of opioid delivery: Systematic literature review of case reports and analysis against a control group

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ABSTRACT

Objective: To investigate the existence of an association between formation of catheter tip intrathecal inflammatory masses with opioid dose and/or concentration.
Methods: A systematic review of catheter tip granulomas case reports and comparison with a control group was carried out. A boolean search was conducted in the electronic databases MEDLINE and EMBASE. The patients' data extracted from the case reports was tested for homogeneity with a control group. Subsequent analysis investigating the association of opioid dose, concentration and flow rate with the formation of catheter tip granulomas was performed.
Results: Seventeen articles resulting in 24 patients with granulomata were included in the review. One patient in our department with granuloma formation was added to this group. Control group comprised 31 patients with an average follow-up of 68.3 ± 9.7 months. The groups were homogeneous considering the variables age, gender and duration of pain previous to implant. Morphine dose ($r = 0.821$, $p < 0.001$) and concentration ($r = 0.650$, $p < 0.001$) were significantly correlated with the development of catheter tip intrathecal masses.
Conclusion: Opioid dose and concentration were significantly associated with the development of catheter tip granulomas. A correlation with opioid concentration was confirmed for the first time.

1. Introduction

Intrathecal spinal analgesia has become a recognized treatment for chronic non-malignant pain since the first reservoir was implanted in 1981 [1]. The use of opioids via intrathecal drug delivery systems (IDDS) allows for a selective concentration to reach an important site of pain transmission, the spinal cord dorsal horn [2]. Opioid administration into the intrathecal space achieves its effects at lower doses than using the epidural route [3]. The drug is highly localized, so its analgesic efficacy is maximized at lower doses [4]. Therefore only a small amount of the drug is systemically absorbed [5]. This leads to a decrease in the possible opioid side-effects.

One of the possible side-effects of intrathecal opioid administration is the development of an intrathecal inflammatory mass, also known as granuloma, granulomata or granulomatous mass. An intrathecal granuloma is a soft tissue mass resulting from an inflammatory reaction usually located at the level of the catheter tip. The formation of a spinal granuloma due to opioid administration using an implanted pump delivery system was first observed in the intrathecal space in 1991 [6]. Although rare, the magnitude of this complication can be serious with potential for neurologic morbidity if not recognized and treated appropriately [7]. The appearance of clinical symptoms can be sudden. The clinical presentation of granulomas is usually marked by an increase in pain while receiving the scheduled medication that previously controlled the painful symptoms and small increases in the dose of intrathecal medication only provide temporarily relief [8].

Intrathecal administration maintains a relatively high drug concentration within and around the spinal cord, which may contribute to the phenomenon of catheter tip mass formation [9]. Inflammatory masses have developed more commonly in result of IDDS therapy involving opioids such as morphine [6], hydromorphone [10], diamorphine [11], fentanyl [12], sufentanil [13] or tramadol [14]. Less commonly, administration of intrathecal baclofen alone has also been related with this complication [15,16].

The association between opioid concentration with the development of catheter tip intrathecal granulomas has only been hypothesized from case reports and animal studies [17]. Animal studies revealed an apparent dose or concentration response in relation to the development of intrathecal masses in both dogs and sheep [18–20]. However, the formation of granulomas in humans is less predictable than in sheep and dog models [17]. Whether the

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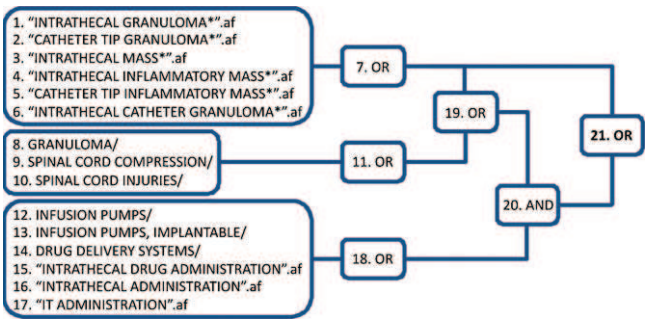

Fig. 1. Diagram of search strategy (MEDLINE).

absolute opioid dose, concentration, or both (or neither) influence a patient's risk for development of a granulomatous mass remains unclear [21].

The aim of this study was to investigate through use of a control group the existence of an association between the formation of catheter tip intrathecal inflammatory masses with opioid dose and/or concentration.

2. Materials and methods

2.1. Experimental design

A systematic literature review of case reports and subsequent analysis by comparison with a control group was performed. This design allows investigation of variables with potential to cause formation of granulomas by comparing a group of patients with this condition with a group of patients undertaking the same therapy but that did not develop this side-effect. Because the majority of granuloma patients were derived from the literature, an investigation of homogeneity of the groups was carried out prior to analysis. To investigate homogeneity of the groups and therefore, suitability for analysis, between group comparisons of the variables age, gender, duration of pain prior to implant and duration of therapy were performed. Moreover, to decrease the influence in the analysis of outliers not caused by sampling or data errors but due to the changes in practice of intrathecal medication dose delivery, a truncation method was used.

2.2. Search strategy

Information on duration of IDDS therapy, dose and concentration of drugs administered at time of diagnosis was sought from granulomatous masses case reports using a boolean search conducted in the electronic databases MEDLINE and EMBASE. A combination of MESH/Thesaurus terms and free text terms was employed according to the database (Fig. 1). The year of publication was restricted to between 1991 (first intrathecal granuloma due to IDDS reported [6]) and 25 August 2010. There were no language restrictions. Hand search of reference lists of included studies, previous reviews and consensus statements was performed. Search sensitivity was checked by ensuring that all articles identified via hand search of reference lists were identified through the structured bibliographic database searches.

2.3. Inclusion and exclusion criteria

Papers were included in the review on the basis that they provided individual information related to dose or concentration of intrathecal opioids administered. Articles were excluded if any of the following was observed: the articles were reviews or guidance papers that did not present original work; morphine dose and/or concentration were presented as group averages instead of individual values; no intrathecal opioid medication had been delivered until granuloma development; the opioids administered are not currently in use at the department from which the control patient group were drawn; infection, tumor or trauma could not be ruled out as the cause of the granuloma reported.

2.4. Control group

Fifty-six patients receiving continuous intrathecal analgesics by implanted reservoir administration at the Midlands in-patient Regional Centre, Dudley, one of the largest UK centres for intrathecal drug therapies. A longitudinal retrospective assessment of medical records was performed and pump refill notes were screened for dose (mg/day), concentration (mg/mL) and flow rate (mL/day) of morphine administered intrathecally. Twenty-four patients were receiving diamorphine and were excluded from the analysis for purposes of comparison. Although diamorphine breaks down to mono-acetyl morphine which in turn breaks down to morphine [22], concentrations and doses are different from morphine. One of the 32 patients receiving morphine had been diagnosed with granuloma formation and was added to the group generated from the systematic review of case reports (see Table 1, RHH).

When attending for pump refill, all patients were asked if the pain was being controlled and if new symptoms had emerged, including new pain, altered sensation, or weakness of limb. In case of an affirmative answer, a neurologic examination took place and if there was a clear change, a magnetic resonance imaging (MRI) scan was performed. For this purpose, programmable pumps were turned off, non-programmable pumps were emptied, and the imaging was carried out via a 1.5 T MRI system through Short Tau Inversion Recovery (STIR) sequence. In the existence of doubts regarding the formation of intrathecal inflammatory masses, a second MRI would be completed with the contrast-enhancing agent Gadolinium.

2.5. Data analysis

Kolmogorov–Smirnov test was performed to test normality of numerical data. Homogeneity of the group of patients diagnosed with granuloma and the control group was tested for the variables age, gender, years in pain prior to IDDS and duration of therapy. Gender differences between the groups were analyzed with Pearson's Chi-Square test. The majority of the numerical data was not normally distributed; therefore differences between patients diagnosed with granuloma and those from the control group were investigated through Mann–Whitney tests. Age was the only variable normally distributed, however to keep uniformity with the other variables, was examined with a non-parametric test. Associations between variables were investigated through Spearman's correlations. Statistical significance represented $p < 0.05$. Means are reported as mean ± standard error of the mean (SEM).

While verifying the distribution of the data, several outliers were identified for the variables dose (all morphine doses ≥32 mg/day) and concentration (all morphine concentrations ≥30 mg/mL). All of these outliers were from data extracted from the literature. Outliers can lead to inflated error rates and substantial distortions of parameter and statistic estimates when using either parametric or nonparametric test [23]. In an effort to reduce the impact of these outliers, increasing the power of nonparametric tests, a truncation method was used [23]. This method was employed as the outliers observed were not caused by sampling or data errors but due to the changes in practice of intrathecal medication dose delivery through awareness of possible complications related with high intrathecal dose and concentration. Because many of the concentrations and doses reported were still higher than the recommended values, we

Table 1
Articles and patients diagnosed with granulomata included in the review.

Author	Gender	Age	Duration of therapy (months)	Drug(s)	Peak concentration (mg/mL)	Peak dose (mg/day)
North et al. [6]	F	42	14	Morphine		120
Aldrete et al. [39]	M	73	3	Morphine	10	11
Blount et al. [40]	M	46	26	Morphine		12
	F	64	24	Morphine		14
	M	38	8	Morphine		19
Cabbell et al. [34]	F	52	8	Morphine		45
	F	39	34	Morphine		28
Anderson et al. [41]	M	61	60	Morphine	50	
	M	65	60	Morphine	50	
McMillan et al. [42]	F	47	16	Morphine + bupivacaine	25	3.5
	F	52	25	Morphine + bupivacaine	75	16
	F	54	18	Morphine + bupivacaine	70	15.8
Shields et al. [43]	M	47	60	Morphine		25
Toombs et al. [44]	F		48	Morphine + clonidine	17.5	15
Miele et al. [45]	M	45	71	Morphine		32
	M	55	10	Morphine		15
Phillips et al. [27]	M	70		Morphine		28
Vadera et al. [46]	M	47	96	Morphine	50	32
Jhas and Tuli [47]	F	54	108	Morphine + bupivacaine + clonidine	30	14
Abejón et al. [48]	M	56	72	Morphine + clonidine		34
Jourdain et al. [49]	M	41	3	Morphine	20	16
Zacest et al. [12]	M	76		Morphine		3.59
De Andrés et al. [37]	F	60		Morphine + bupivacaine + clonidine	40	17
Hoederath et al. [38]	F	52	20	Morphine		11
RHH	F	59	21	Morphine + bupivacaine	10	6.5

used the recommended values derived from an expert panel [17], and the maximum values for morphine dose and concentration subsequent to truncation of the data were 15 mg/day and 20 mg/mL respectively.

Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) software (version 17.0, SPSS Inc., Chicago, IL, USA). Post hoc power analyses were performed using G*Power 3.1.2 software [24].

3. Results

3.1. Systematic literature review

The search resulted in a total of 771 abstracts after removal of duplicates. Following screening of abstracts and hand search of reference lists, 32 articles were retrieved for review (Fig. 2).

Articles were excluded after review for not presenting information regarding dose or concentration administered [25–28]; there were no opioids included in the intrathecal medication [15,16,29]; the opioids were hydromorphone [10,12,27,30–32], fentanyl [12], sufentanil [13] or tramadol [14] which are currently not administered in the institution where the control group is followed; the granuloma could be result of infection, tumor or trauma [33–36]. Seventeen articles resulting in 24 patients with information regarding dose and/or concentration of intrathecally administered morphine were included in the analysis (Table 1). In reports where a reoccurrence of a granulomatous mass was observed [34,37,38], only the morphine dose and/or concentration until the formation of the first mass were considered.

Eight of the studies reported a rapid increase in the morphine dose previous to diagnosis [6,27,34,38,40,41,44,45].

The subjects identified in the case reports in addition with the patient from our department, comprised 13 males (52%) and 12 females (48%) with an average age at the moment of diagnosis of 54 ± 1.9 years (range: 38–76). The average duration of treatment until intrathecal inflammatory mass formation was 36.6 ± 6.5 months (range: 3–108) and the mean peak dose and concentration were respectively 23.19 ± 4.9 mg/day (range: 3.5–120) and 37.29 ± 6.37 mg/mL (range: 10–75). Following truncation

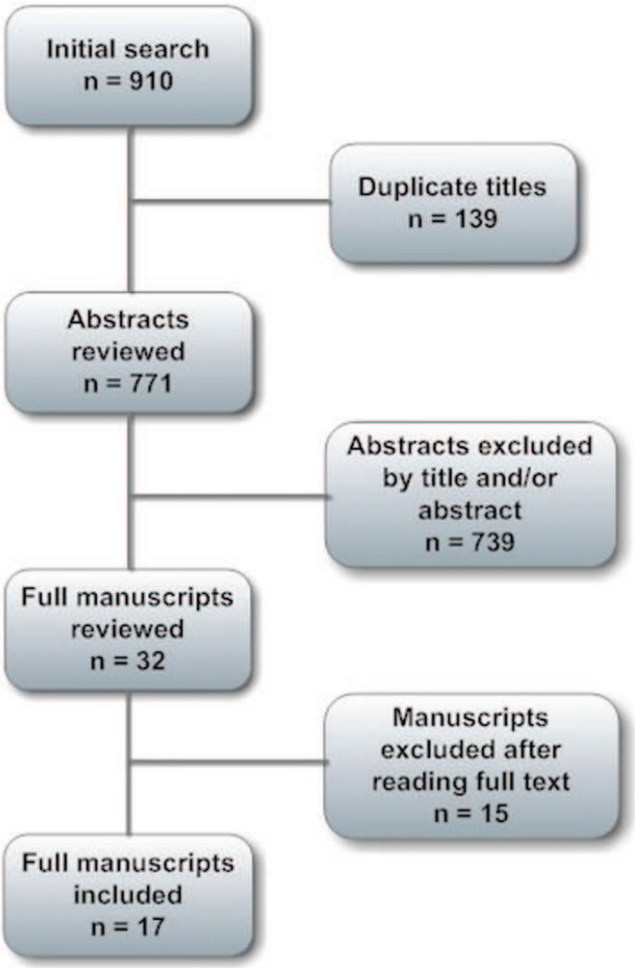

Fig. 2. Flow diagram illustrating the literature search results.

Table 2
Characteristics of patients included in the control group.

Patient ID	Gender	Age	Duration of therapy (months)	Drug(s)	Peak concentration (mg/mL)	Peak dose (mg/day)
1	F	69	33	Morphine	6.00	1.73
2	F	48	121	Morphine	2.00	3.00
3	F	42	108	Morphine + bupivacaine	10.00	4.00
4	M	45	32	Morphine	12.00	6.13
5	M	54	24	Morphine	6.00	1.83
6	M	47	62	Morphine	6.00	0.85
7	F	57	42	Morphine + clonidine	6.86	3.43
8	F	66	10	Morphine	8.00	2.75
9	F	62	25	Morphine + bupivacaine	4.00	1.60
10	M	32	80	Morphine + bupivacaine	11.10	3.50
11	F	40	73	Morphine + bupivacaine	3.43	1.44
12	F	45	115	Morphine + bupivacaine	10.00	2.25
13	F	57	85	Morphine	8.00	2.83
14	F	30	149	Morphine + bupivacaine + clonidine + baclofen	5.71	2.80
15	F	52	9	Morphine	12.00	5.50
16	F	70	49	Morphine	8.00	3.00
17	M	63	81	Morphine	11.10	3.00
18	M	34	203	Morphine + bupivacaine	2.29	1.14
19	F	72	26	Morphine + bupivacaine	18.00	6.88
20	M	52	202	Morphine + clonidine	8.57	4.29
21	F	46	13	Morphine	6.00	2.50
22	M	57	19	Morphine	5.00	3.13
23	F	56	25	Morphine	6.00	2.50
24	F	38	42	Morphine	5.70	2.86
25	F	45	30	Morphine	1.70	0.86
26	M	50	13	Morphine	4.00	1.50
27	F	60	50	Morphine	6.00	2.20
28	M	44	131	Morphine	5.70	2.83
29	F	39	108	Morphine + bupivacaine + clonidine + baclofen	2.00	3.00
30	M	54	43	Morphine	9.00	4.50
31	F	46	114	Morphine + bupivacaine	5.00	1.85

of data, the mean peak dose and concentration were respectively 13.06 ± 0.76 mg/day (range: 3.5–15) and 18.12 ± 1.11 mg/mL (range: 10–20).

3.2. Control group

The control group consisted of 11 males (35.5%) and 20 females (64.5%) (Table 2). The mean age in this group was 50.7 ± 1.9 years (range: 30–72) and the average follow-up period post implant was 68.3 ± 9.7 months (range: 9–203). The mean peak opioid dose was 2.89 ± 0.26 mg/day (range: 0.85–6.88) and the average peak concentration was 6.94 ± 0.64 mg/mL (range: 1.70–18). Eleven of these patients had crossed over from diamorphine to morphine during their treatment. In addition to the patients who developed a granuloma, 16% of the remaining patients presented clear changes in their pain including new symptoms. Following a magnetic resonance imaging (MRI) scan, no masses were detected in these patients.

3.3. Homogeneity between groups

Demographic differences between patients diagnosed with granuloma (GG) and the control group (CG) were investigated prior to analysis, to confirm if these could be compared (Table 3).

No significant differences were observed in age, gender and duration of pain prior to IDDS between granulomata patients and the control group. The number of months with IDDS in the CG ($Mdn = 49$) was significantly longer than the duration of treatment of patients in the GG ($Mdn = 24.5$), $U = 203.5$, $p < 0.05$, $r = -0.34$. This was not considered as an impediment for analysis as the risk of developing an inflammatory mass increases with the duration of intrathecal therapy. The incidence has been reported as 0.04% after 1 year, increasing to 1.15% after 6 years [19].

3.4. Associations with granuloma formation

Both morphine dose ($r = 0.821$, $p < 0.001$) and concentration ($r = 0.650$, $p < 0.001$) were significantly associated with the development of intrathecal masses.

The morphine concentration was significantly higher in the GG ($Mdn = 20.0$) than in the CG ($Mdn = 6.0$), $U = 13$, $p < 0.001$, $r = -0.72$ (Fig. 3). The morphine dose in the GG ($Mdn = 15$) was significantly higher than in the CG ($Mdn = 2.82$), $U = 13.5$, $p < 0.001$, $r = -0.82$ (Fig. 4). Post hoc power analyses were performed indicating a power of 81% for dose administered and a power of 52%.

It should be noted that the outliers in Figs. 3 and 4 representing elevated values (although lower than the

Table 3
Analysis of demographic differences between patients diagnosed with granulomas and control group produced from patients' notes.

Variable	Granuloma group ($N = 25$)	Control group ($N = 31$)	Test statistic	p value	Statistical test
Age[a]	54 ± 1.9 (38–76)	50.7 ± 1.9 (30–72)	−1.002	0.321	Mann–Whitney
Gender	M (13); F (12)	M (11); F (20)	$\chi^2(1) = 1.542$	0.280	Chi-Square
Duration of pain previous to IDDS[a]	11.7 ± 1.7 (3–20)	14.3 ± 1.7 (2–36)	−0.384	0.711	Mann–Whitney
Months with IDDS	36.6 ± 6.5 (3–108)	68.3 ± 9.7 (9–203)	−2.483	<0.05	Mann–Whitney

[a] Years.

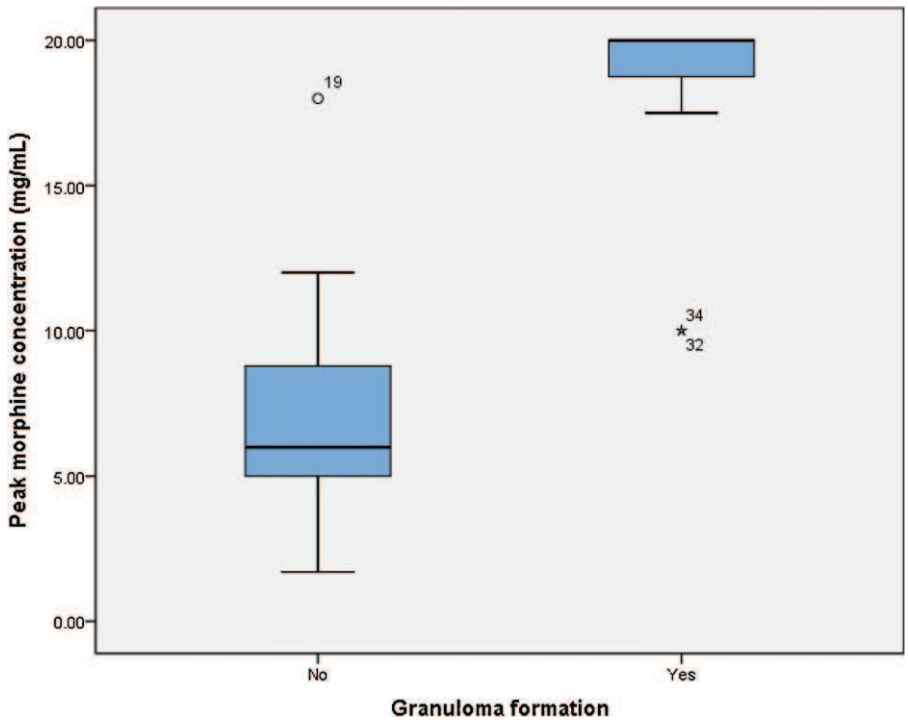

Fig. 3. Peak morphine concentration and granuloma formation. ○ indicates an outlier ≥1.5 and <3 times the value of the interquartile range; * indicates an outlier ≥3 times the value of the interquartile range.

recommended values) were observed for the group without granulomas and outliers representing low scores were only observed for the patients diagnosed with granuloma. This means that the impact of excluding these outliers would increase the positive correlation of concentration and dose with the formation of granulomata.

The relative risk of developing a granuloma increases with dose and concentration (Tables 4 and 5). Although possible, the risk of granulomata is lessened with lower doses and concentrations.

Flow rate and catheter tip location were not found to be associated with the formation of intrathecal inflammatory masses ($p > 0.05$).

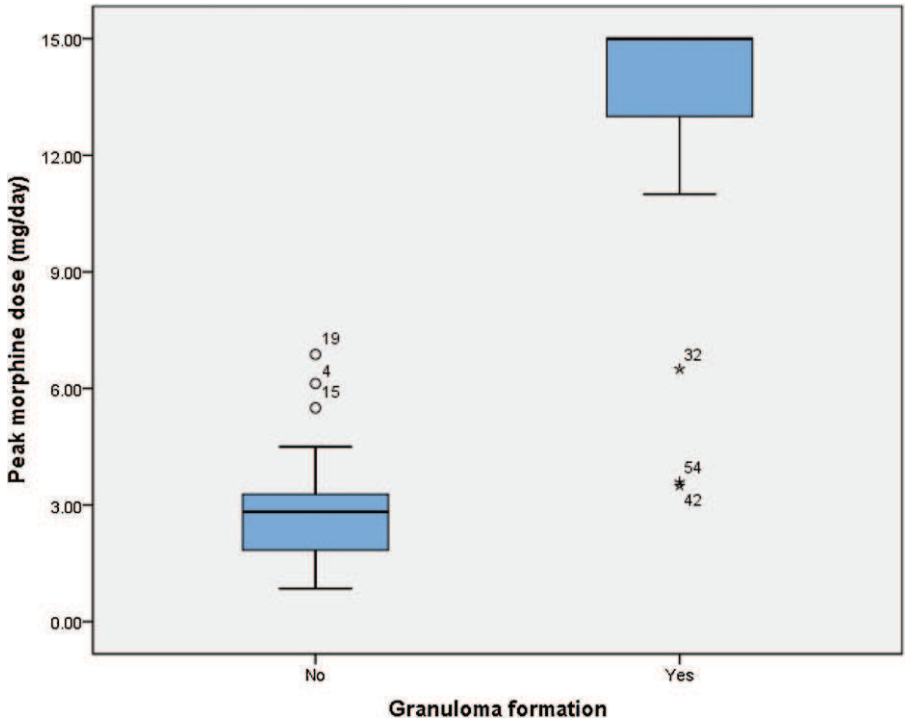

Fig. 4. Peak morphine dose and granuloma formation. ○ indicates an outlier ≥1.5 and <3 times the value of the interquartile range; * indicates an outlier ≥3 times the value of the interquartile range.

Table 4
Morphine dose and relative risk of granuloma formation.

Morphine	Granuloma ($N = 23$)	No granuloma ($N = 31$)	Total	Relative risk
Dose < 5 mg/day	2	28	30	0.066
Dose ≥ 5 mg/day	21	3	24	0.875
Dose < 10 mg/day	3	31	34	0.088
Dose ≥ 10 mg/day	20	0	20	1
Dose < 15 mg/day	8	31	39	0.205
Dose ≥ 15 mg/day	15	0	15	1

Table 5
Morphine concentration and relative risk of granuloma formation.

Morphine	Granuloma ($N = 12$)	No granuloma ($N = 31$)	Total	Relative risk
Concentration < 10 mg/mL	0	25	25	0
Concentration ≥ 10 mg/mL	12	6	18	0.666
Concentration < 15 mg/mL	2	30	32	0.062
Concentration ≥ 15 mg/mL	10	1	11	0.909
Concentration < 20 mg/mL	3	31	34	0.088
Concentration ≥ 20 mg/mL	9	0	9	1

4. Discussion

Opioid dose and concentration were found in this study to be associated with the development of catheter tip granulomas indicating that this link might be more causal than casual.

The mean peak morphine dose of 3 mg/day at an average follow up of 70 months in our patient group was lower than previously reported doses of 4.7 mg/day after an average of 3.4 years [5]; 7.42 at 29.14 months [50]; 9.6 mg/day at 1 year [51], 9.8 mg/day [34] and 21 mg/day at 52 weeks [52]. However, it is important to state that with the exception of the Yaksh and Onofrio paper [52] which was published before the first case report of an intrathecal granuloma, the opioid doses reported are significantly lower, even after truncation of data, than those of the patients with granulomata and therefore significant differences would also be observed between these cohorts and the patients diagnosed with granuloma.

Opioid dose has previously been suggested to be associated with intrathecal inflammatory masses formation [42,53]. Coffey and Burchiel following observations on 41 cases of granulomata, including 16 from the literature suggested the administration of relatively high concentration or high dose opiate drugs as one of the most plausible hypothesis with regard to the formation of intrathecal catheter tip mass lesions [9]. Concentration rather than daily dose has been suggested to be the primary contributing factor in the development of these masses [54]; however, a significant association had not yet been established in human data. In this study, significant differences between the groups were verified despite the effect size being more elevated for opioid dose. This may be due to the fact that it might be more usual to adjust the delivered dose than to alter the drug concentration when responding to patients' level of pain to obtain a compensatory flow rate change in the commonly used programmable pumps. This would also explain why in the McMillan et al. [42] and Duarte et al. [53] studies an association with concentration was not verified.

The influence of dose and concentration applies only to catheter tip granulomas. When the mass is a consequence of an infection or reaction to catheter material, sometimes the granuloma can be traced along the length of the catheter [26].

Flow rate was not found to be significantly associated with the development of catheter tip granulomas, possibly due to the flow rate being computed with the peak concentration and peak dose values. Throughout the course of treatment the flow rate was likely to change when concentration, dose or both were altered. Ultra slow flow rates are advised to be avoided and the drugs delivered into the dorsal cerebrospinal fluid space at L1–L2 or T7–T10 to prevent the formation of intrathecal inflammatory masses [17].

An association between catheter tip location and development of inflammatory masses was not established in this study. This can be related with the fact that most implanters position the catheter tip in the thoracic level [19], even though these masses have been known to form at all levels of the intrathecal space [17].

The identification of this complication in its early stages is imperative and determinant to reduce the magnitude of the consequences. Forty per cent of the reports mentioned a rapid increase in the dose administered was observed prior to granuloma diagnosis. The development of a granuloma reduces the efficacy of the intrathecal medication [55] and the failure to identify the occurrence of a granuloma can lead to a diagnosis of tolerance and an increase in the rate of infusion [25,41]. Although this lesion develops very slowly, patient re-evaluation and vigilance are essential for an early diagnosis [16]. MRI remains as the gold standard for diagnosing intrathecal inflammatory masses; however, routine imaging in all patients with intrathecal pumps is not cost-effective taking into consideration the low occurrence of granulomas and the elevated cost of an MRI [56]. Pump refills have been suggested as a good opportunity to examine patients' lower extremity motor, sensory and reflex function [39]. The yearly opioid dosage change can be used as an early indicator of the formation of granulomas [53]. If new pain symptoms are observed alongside clear changes in intrathecal medication requirements, an MRI or as an alternative a computed tomography myelogram should follow [17].

Both dose and concentration should be kept as low as possible to reduce the relative risk of granulomata. The relative risk can be almost halved by reducing dose and concentration from the currently recommended maxima of 15 mg/day and 20 mg/mL to 10 mg/day and 15 mg/mL respectively. These doses are still higher than the average reported to obtain an optimal pain control [5,34,50,51]. Patients that require high doses should be adequately informed of the risk of granuloma formation and what signs and symptoms might occur [45,57]. When the maximum recommended values for dose and concentration do not generate the desired pain relief, Ziconotide should be taken into consideration as an alternative intrathecal medication. To date there are no reports associating this drug with the occurrence of catheter tip granulomas and its use has been recommended in the 2007 polyanalgesic consensus conference algorithm for intrathecal drug selection [58].

The findings, though significant have to be considered against the background of the limits of the study. In our department, besides the morphine patient diagnosed with granuloma formation, 16% of the remaining patients had presented clear changes in their pain including new symptoms but were not found to have developed this complication following MRI screening. Despite not

all the patients in the control group being screened for granulomata using an MRI scan, the rate of this diagnosis has been reported to be the equivalent to 0.009 events per patient year [53], which means it would have little or no statistical impact in the analysis.

The analysis is also limited by the exclusion of patients diagnosed with inflammatory masses not being administered morphine as the intrathecal medication. We considered that for the purpose of comparison, it would be preferable to only include patients undertaking an identical intrathecal therapy. Therefore, we cannot ascertain if the same results would be verified with other opioids not investigated in this study. Compounding pharmacy and co-analgesics may also have a greater role in the development of granulomas and therefore may be confounders.

One of the limitations of this study is the fact that the control group is based on a single centre cohort. A large multi-center study is warranted not only to confirm these findings, but also to investigate other hypotheses as to the etiology of granulomas, including dose and concentration of other intrathecal agents, flow rate, catheter tip design and location. An analysis of the dose, concentration and flow rate throughout duration of treatment instead of peak values would shed more light on the role of intrathecal medication in the formation of granulomas.

This is the first review of case reports performed in a systematic method studying the influence of opioid dose and concentration in the development of catheter tip intrathecal inflammatory masses. The comparison with a control group allowed for the first time to statistically confirm a long-standing inference that concentration plays an important role in the formation of granulomas. Additionally, significant differences were observed for dose administered corroborating results of previous studies.

The relative risk can be decreased by reducing dose and concentration from the currently recommended maxima of 15 mg/day and 20 mg/mL to 10 mg/day and 15 mg/mL respectively.

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