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Qualification en INDIQUER VOTRE SPÉCIALITÉ DE D.E.S.

Preventing Post Dural Puncture Headache after Intrathecal Drug Delivery System Implantation through Preventive Fibrin glue Application : a retrospective study

Prévention des maux de tête post-ponction lombaire après l'implantation d'un système d'administration intrathécale de médicaments grâce à l'application préventive de colle de fibrine : étude rétrospective

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Liste des Abréviations :

LCR : liquide céphalo-rachidien

SPPL : syndrome post ponction lombaire

CIT : cathéter intra-thécal

C- : sans colle biologique

C+ : avec colle biologique

IDDS : Intrathecal drug delivery systems

AEs : Adverse effects

CSF : Cerebrospinal Fluid

PDPH : Post-Dural Puncture Headache

SCS : Spinal cord stimulation

Plan

Preventing Post Dural Puncture Headache after Intrathecal Drug Delivery System Implantation through Preventive Fibrin glue Application: A Retrospective Study

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1. Résumé

Contexte : Les fuites de liquide céphalo-rachidien (LCR) peuvent entraîner un « syndrome post ponction lombaire » (SPPL). Cet effet secondaire est fréquemment observé après mise en place d'un cathéter intra-thécal (CIT). Ce syndrome post ponction lombaire affecte la qualité de vie des patients et peut entraîner d'autres complications. La colle biologique est utilisée pour traiter les fuites de LCR. Nous avons développé une méthode pour réduire l'incidence de ces céphalées par l'administration de colle biologique pendant la mise en place du CIT.

Objectif : le critère de jugement principal était l'incidence du SPPL après implantation du CIT avec ou sans colle biologique.

Design : Étude monocentrique rétrospective comparant 2 cohortes de patient bénéficiant de la mise en place d'une pompe intrathécale avec ou sans colle biologique sur 2 périodes successives.

Méthode : Introduction de la colle au contact de la zone de ponction lors de la mise en place du cathéter, après retrait de l'aiguille de ponction.

Résultat : Nous avons réuni 107 patients sans colle biologique (C-) et 92 avec colle (C+), avec à noter deux échecs d'administration. L'application de colle entraîne une diminution significative de l'incidence du SPPL, de 32,7% dans le groupe C- à 10,92% (p <0,001) dans le groupe C+. En ce qui concerne la sévérité, dans le groupe C-, 37,1% des SPPL étaient légers, 34,3% modérés et 28,6% sévères. Dans le groupe C+, 80% des SPPL étaient légers, 20% modérés et 0% sévère. La durée des symptômes était statistiquement plus courte dans le groupe C+ (maximum de 3 jours, contre 15 jours dans le groupe C-). En

analyse univariée, l'application de colle et l'âge étaient significatifs pour prévenir le SPPL. En analyse multivariée, seul l'application de colle était significative (OR = 0.26 p = 0.0008). Nous n'avons pas observé d'effets secondaires liés à l'application de colle biologique.

Limite : Le caractère rétrospectif et monocentrique entraine un risque de biais de sélection et d'effet centre.

Conclusion : L'utilisation de colle biologique est prometteuse en terme d'efficacité et de sécurité pour limiter les syndromes post ponction lombaire après mise en place d'un cathéter intra-thécal par voie chirurgicale. Son coût modéré et sa reproductibilité en font une technique abordable et efficace.

2. Introduction

Intrathecal drug delivery systems (IDDS) are increasingly recommended for treating refractory cancer related pain (1). Although their efficacy is well-established (2) adverse effects (AEs) can occur in the fragile population. Cerebrospinal Fluid (CSF) leakage is often observed in the immediate postoperative phase, up to 23% in one series (3,4) and leads to a debilitating Post-Dural Puncture Headache (PDPH). Though spontaneous resolution is common, occasionally PDPH results in additional complications such as subdural hematoma secondary to intracranial hypotension(5), or a chronic fistula development, causing a long term headache and/or subcutaneous hygroma(4). Thus, IDDS can paradoxically worsen quality of life instead of improving it, due to this iatrogenic complication. Accidental CSF puncture can also occur after spinal cord stimulation (SCS) implantation (6)

Traditional treatment of PDPH (7,8) with blood patches is effective (9). However, after IDDS implantation, risk of infection around a fresh incision, and other risks such as catheter damage or puncture, limit its usefulness.

In this context, finding and implementing preventive measures seem essential. The reduced incidence of PDPH after lumbar puncture for spinal anesthesia using small-diameter (10) or atraumatic needles (8) is well known. In IDDS implantation, a 16 G introducer needle is necessary, and this diameter cannot be changed. Additionally, the catheter diameter is smaller than that of the needle, hence some CSF leakage is inevitable. A purse string suture in the soft tissues is the manufacturer recommended method of prevention, however this is not foolproof (11). Tisseel is authorized for application in neurosurgery as a tissue glue to promote dura sealing (12). Animal studies established no toxicity on nerve structures (13,14). An animal study in swine concluded that percutaneously injected fibrin glue is effective in stopping CSF leaks after dural puncture in this animal model (15). In addition, a recent literature review (33 publications), specifically examining the effect of fibrin glue on

dura sealing proved the efficiency in dura sealing and observed no toxicity to the spinal cord or the nerves (16). In the last decade, Fibrin glue has been used by neurosurgeons to control CSF leakage after intraoperative dural puncture or tear (17). There are many reports of this from as early as 1999 (18). A recent review focused on dural repair with four spinal sealants or fibrin glues (19) concluded that Tisseel, has been used in many large clinical series without adverse events. Despite the lack of FDA approval, Tisseel (fibrin glue) has seen wide adoption in "off-label" use. In fact, previous large series from the Mayo clinic for CSF leaks advises use of fibrin sealeant in refractory CSF leaks where the first blood patch has been ineffective (20). Moreover, in a recent publication after a systematic review including 16 studies, it was concluded that use of fibrin glue was equal if not superior to the micro suturing of nerves (21).

A recent small series of 3 patients reports treatment of chronic CSF leakage post-implantation of IDDS catheter by epidural injection of 3 to 10 ml of fibrin glue well after implantation (22). In one large retrospective series of IDDS implantation at an academic medical center the incidence of PDPH was 23%, and only 21% of this group needed an epidural blood patch or epidural fibrin glue (23).

In this context, we have examined the prophylactic use of Fibrin Glue to prevent CSF leakage during intrathecal catheter implantation, and thereby reduce the incidence of PDPH. At our institution, the standard of care was changed in Mar 2018 to include the prophylactic use of Fibrin Glue. Hence this provided a natural division of the patient population into two cohorts; a before (No Glue) group and an after (Glue group). Our retrospective study examines these two cohorts with reference to the incidence, duration, and severity of PDPH, resulting from CSF Leakage syndrome.

3. Material and Methods

3.1. Study design:

We designed an observational retrospective cohort study, in order to compare the incidence of PDPH syndrome after lumbar puncture in patients implanted with an intrathecal pump, with or without preventive Fibrin Glue application during the procedure. The study compared two patient cohorts over two successive periods: during the first period from January 2017 to February 2018, patients did not receive Fibrin Glue; during the second period, from March 2018 to April 2019, patients received preventive application of Fibrin Glue.

3.2. Statement of study approval:

The local Ethics Committee of Angers (N ° 2019/51) validated the study protocol. Following the new French law for retrospective studies, the committee required that an information letter to be sent to all patients alive as of May 1st, 2019, allowing them to refuse use of their data in our study. The information letter was sent on May 2019.

3.3. Population:

All successive patients that were implanted with IDDS at the Institute of Cancerology of the West between January 2017 and April 2019 were included. There were no exclusion criteria. All the living patients agreed to participate.

3.4. Fibrin Glue:

Tisseel Bioglue (Baxter SAS___ 78280 Guyancourt France) is an association of human fibrinogen, synthetic aprotinin, human thrombin, and calcium chloride. These substances are packaged in two separate syringe compartments and are mixed to make the final product when injection is performed, with the aid of the delivery system (Figure 1). The mix rapidly coagulates (24,25). This product is indicated to promote healing and coagulation during surgery in Europe by European Medicinal Agency (26). In UK, one specific indication is : "to promote adhesion/sealing in neurosurgery where contact with cerebro-spinal fluid or dura mater may occur" (12). Intravascular injection is not recommended. This product by Tisseel® has frequently been used to repair injury in pia mater (19), even if its use for this indication has not been recommended in the USA by the FDA.

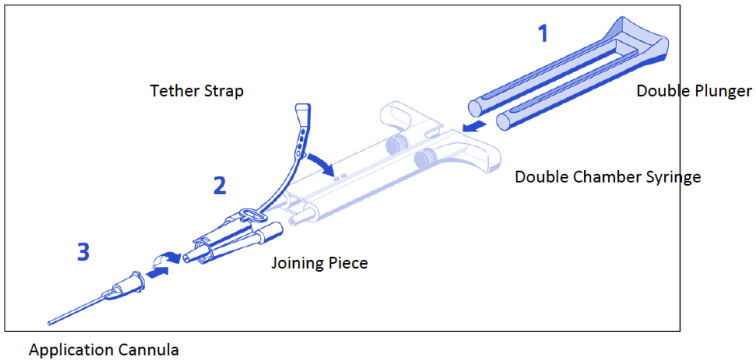

Figure 1 : Fibrin Glue Application device

3.5. Technical features:

Implantation of intrathecal pumps (IDDS) was conducted by four different physicians, all trained in the technique, at the Institute of Cancerology of the West in Angers (France). The procedure consists in intrathecal space catheterization by lumbar puncture between L1-L2 and L4-L5 using a 16G Tuohy needle followed by Ascenda® (Medtronic 92100 Boulogne Billancourt – France) catheter insertion with tip placement at the desired vertebral level, depending on pain location, under fluoroscopic guidance. We have developed an original

procedure for Fibrin glue application during intrathecal catheter implantation. Tisseel Bioglue is injected into the introducer needle puncture pathway, after placement of the catheter, immediately following needle removal. The procedure is performed just before anchoring the catheter with the help of the anchorage device. The puncture pathway is found using the application cannula of Fibrin Glue adjacent to the catheter. The cannula is then inserted into the track of the puncture needle thus located. The canula is then gently pushed along the catheter to the depth of the epidural space as measured by the length of the needle needed to reach the intrathecal space and stopping short. The canula crosses the length of the Spinous Process (Interspinous Ligament and Ligamentum Flavum) to the depth of the epidural space as measured by the length of the needle. In a recent publication, the length of the spinal process was on average 25.6 mm +/- 5.96 (27). Therefore, the 30 mm long cannula is appropriate. When the cannula is not in the space, the injection is challenging with high pressure and/or a backflow observed around the catheter, and it should be repositioned. Then, 3ml of Fibrin glue, is injected as the application cannula end is slowly removed, while verification is made that there is no glue backflow. The volume was chosen following Garcıa-Aguado publication (1.4 ml for Swine) (15), taking into account the diameter of the puncture of the dura by the needle and the need to avoid potential compressive complications on the spinal cord. (Figure 2)**.**

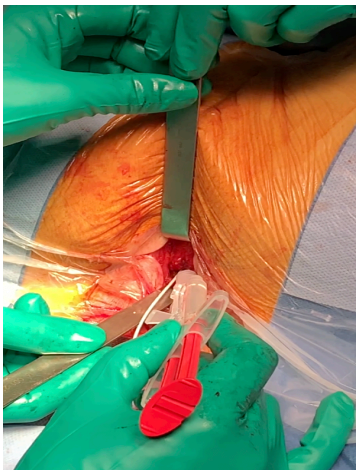

Figure 2 : Fibrin Glue application

3.6. Data sources :

Data for this study were collected from electronic patient records including demographics, treatment indication, puncture level, and catheter tip level. Length of hospital stay, both in total and after implantation, and costs of hospitalization, were also collected. Data relating to PDPH, such as PDPH intensity, neck pain, nausea, vomiting, sweating, diplopia etc has been systematically collected on a daily basis as a matter of protocol in our institution, since 2015 by nurses and other caregivers on electronic records, for all patients receiving IDDS. Data was gathered by two physicians working independently. Finally, a validation meeting was held to discuss the issues for cases where the two physicians were in disagreement over the presence or absence of PDPH, or over intensity or duration of symptoms to rule on each case (N=12) (Table 1). An agreement was found on each challenging case following the Lybecker ladder (28) (Table 2)

concertation meeting results modifications	N
moderate to severe	4
Severe to moderate	3
Moderate to mild	2
mild to moderate	1
Symptom duration (3 patients with also a change in symptom intensity)	4

Table 1 : Data modifications after concertation meeting

	Physical activity	***Confined to bed***	***Associated Symptoms***
Mild	slight restriction	No	No
Moderate	Restricted activity	Part of the day	Not necessarily present
Severe	Bedridden	for the entire day	Always present

Table 2 : Lybecker ladder (28)

3.7. Outcomes:

3.7.1. Primary outcome

The main outcome criterion for this study was the incidence of Post Dural Puncture Headache syndrome after IDDS implantation. PDPH was observed for during the first 7 days after implantation.

3.7.2. Secondary outcome

When PDPH was found, duration and intensity information was recorded. Patients who presented with PDPH were placed into one of three categories, based on intensity (Lybecker Scale): Mild, Moderate, or Severe (28). Duration of symptoms were also analyzed, and adverse effects of Fibrin glue application (if any) was noted (allergy, motor and sensory effects, infection). The association between Fibrin glue utilization and overall survival was also investigated. Finally, length of hospital stay was analyzed after pump implantation, as well as costs of hospitalization.

3.8. Statistical analysis:

The distribution of quantitative data was summarized by median, interquartile range (IQR, i/e, 25e-75e percentile) and range. Comparisons between groups were realized with Student t test or Mann Whitney test according to the application condition of these tests. Binary and categorical data were presented using number and percentage of available values. Comparisons between groups were tested using Chi-square test of Exact Fisher test if appropriate. Overall survival was defined by the time between date of Pump implantation and date of death, or last follow-up. Survival times estimations and survival curves were computed using Kaplan-Meier method. No imputation of missing data was realized. All tests were bilateral a p-value lower than 0.05 was considered as statistically significant. Statistical analyses were conducted using R software, version 3.5.1.

4. Results:

A cohort of 199 consecutive patients receiving intrathecal analgesia IDDS between January 6th, 2017 and March 28th, 2019. From January 6th, 2017 to March 1st, 2018, catheter positioning was performed without Fibrin Glue application. From March 1, 2018 onwards, Fibrin Glue was applied to all patients except two (due to the inability of introducing the cannula into the pathway) during IDDS implantation. These 2 patients were included in the No Glue group. The No-Glue group numbered 107, while the Glue group numbered 92. Basal characteristics of patients except age (Table 3) were not significantly different.

All patients presented with Stage 4 metastatic cancer, primarily of the digestive tract (36.7%). Other locations of origin were: broncho-pulmonary (19.6%), prostatic (11.6%), breast (8%). Catheter tip level varied from T11 to the Cisterna Magna, depending on pain location.

Intrathecal analgesic drug administration was carried out using an intrathecal internal pump (Synchromed II) ◦ in 92.5% of cases, and an external pump connected to a subcutaneous port for 7.5 %. Within the Fibrin Glue group an internal pump was implanted for 91.3 % of patients and in the No Glue Group for 93.5 % of patients.

		All N=199	No Glue N=107 (53.8%)	Fibrin Glue Yes N=92 (46.2%)	p-value
Sex	Male	114/19 (57.3%)	58/107 (54.2%)	56/92 (60.9%)	0.42
	Female	85/199 (42.7%)	49/107 (45.8%)	36/92 (39.1%)	
OME*	Min.- Max	60-4600	75-3400	60-4600	0.22
	1st Qu.-3^{e} Qu	300-600	300-720	300-555	
	Median	360	400	360	
	NA's	1	1	0	
Age	Min. - max	19-89	30-88	19-89	**0.0194**
	1st Qu.-3^{e} Qu	57-71	54.5-69	58-74	
	Median	63.50	61	64	
	NA's	1	1		

Table 3 : Demographic characteristics ** OME = Oral Morphine Equivalent (22)*

4.1. Primary outcome:

Concerning the primary outcome criterion, namely the presence of CSF leakage syndrome and resulting PDPH, the use of Fibrin Glue during the procedure resulted in a significant decrease in incidence, from 32.7% in the No Glue group to 10.92 % (p<0,001) in the Fibrin Glue group (Table 4)

		All cohort N=199	No Glue N=107 (53.8%)	Fibrin glue yes N=92 (46.2%)	p-value
Headache	No Yes	154/199 (77.4%) 45/199 (22.6%)	72/107 (67.9%) 35/107 (32.7%)	82/92 (89.1%) 10/92 (10.9%)	**0.0002**
Severity	Mild PDPH Moderate PDPH Severe PDPH	21/45 (46.7%) 14/45 (31.1%) 10/45 (22.2%)	13/35 (37.1%) 12/35 (34.3%) 10/35 (28.6%)	8/10 (80%) 2/10 (20%) 0/10	**0.040**
Duration	Min.-Max 1st Qu.-3eQ Median	1.5-15 3-5 3	1.5-15 3-5.7 4	2-3 2.25-3 3	**0.0153**

Table 4 : PDPH incidence, severity and duration

4.2. Secondary outcomes:

Concerning symptom intensity, we observed difference between the two groups, with a significant lower rate of severe PDPH in the Fibrin Glue group. According to the Lybecker Scale, in the No-Glue group, 37.1% of PDPH Syndromes were Mild, 34.3% were Moderate, and 28.6% were Severe. In the Fibrin Glue group, 80% of PDPH syndromes were Mild, and 20% were Moderate. No PDPH of severe intensity were reported when Fibrin Glue was applied. Duration of symptoms was also statistically shorter in the Fibrin Glue group (maximum of 3 days, versus 15 days in the No-Glue group), with a median value of 3 in the Fibrin Glue group versus 4 for the No-Glue group (p = 0.0153).

Nausea, which is the second most frequent symptom associated with PDPH(30), is overrepresented in the No-Glue group (34.6% vs 20.7% (p = 0,021) (Table 5).

18.7% of patients in the No-Glue group presented vomiting, while only 10.8% did so in the Fibrin Glue group (p=0.11). Sweating (34.6% versus 25%, p = 0,13), was also higher in the No-Glue group versus the Fibrin Glue group but results were not significant. It should be also noted that post-operative diplopia was found in 4.7% of the No-Glue group versus 3.3% of the Bio-Glue group (p = 0.72).

		No Glue N=107 (53.8%)	Fibrin Glue Yes N=92 (46.2%)	p-value
Sweating	No	69/107 (64.5%)	69/92 (75%)	
	Yes	37/107 (34.6%)	23/92 (25%)	0.13
Nausea	No	66/107 (61.7%)	72/92 (78.3%)	
	Yes	37/107 (34.6%)	19/92 (20.7%)	0.021
Vomiting	No	83/107 (77.6%)	81/92 (88%)	
	Yes	20/107 (18.7%)	10/92 (10.8%)	0.11
Diplopia	No	98/107 (91.6%)	89/92 (96.7%)	
	Yes	5/107 (4.7%)	3/92 (3.3%)	0.72

Table 5 : Symptoms associated sorted by Fibrin Glue application or Not

On the other hand, analysis of data from the two groups combined (Table 6), shows statistically higher rates of sweating in headache-afflicted patients (55.6% versus 22.7%, p<0,0001), higher incidence of vomiting (35.6% versus 9.1%, p<0,0001), and higher rates of nausea (68.9% versus 16.2%, p<0,0001) and vomiting.

		No Headache N=154	Headache N=45	p-value
Sweating	No	119/154 (77.3%)	19/45 (42.2%)	
	Yes	35/154 (22.7%)	25/45 (55.6%)	<0.0001
Diplopia	No	148/154 (96.1%)	39/45 (86.7%)	
	Yes	4/154 (2.6%)	4/45 (8.9%)	0.07
Nausea	No	126/154 (81.8%)	12/45 (26.7%)	
	Yes	25/154 (16.2%)	31/45 (68.9%)	<0.0001
Vomiting	No	137/154 (89%)	27/45 (60%)	
	Yes	14/154 (9.1%)	16/45 (35.6%)	<0.0001

Table 6 : Symptom associated sorted by PDPH or not

4.3. Predicting PDPH factors:

3 factors were analyzed for PDPH occurrence. In a univariate analysis preventive Fibrin glue application and age were statistically significant. In multivariate analysis only fibrin Glue application was found to be significant (OR = 0.26 p = 0.0008) (Table 7)

	Univariate		Multivariate	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Preventive Glue application	0.25 (0.46-0.54)	0.0004	0.26 (0.12-0.57)	0.0008
Implantation age	0.97 (0.97-0.99)	0.0221	0.97 (0.94-0.99)	0.0266
Internal Pump versus external pump	0.24 (0.13-1.92)	0.1809	0.24 (0.03-2.01)	0.1898

Table 7 : Predicting PDPH factors

4.4. Survival:

In this cohort of patients treated for pain through intrathecal analgesia, median survival time is 2.9 months (95% CI: 2.3-3.9). There is no difference between patients receiving prophylactic Fibrin Glue at implantation (2.9 months, 95% CI: 1.7-6.5) and those not

receiving Fibrin Glue (2.8 months, 95% CI: 2.3-4. p=0.60). Onset of headaches is not significantly associated with a difference in survival time (2.8, 95% CI: 2.3-4, p=0.60) but the Fibrin glue group was implanted the year after No-glue group (Figure 3).

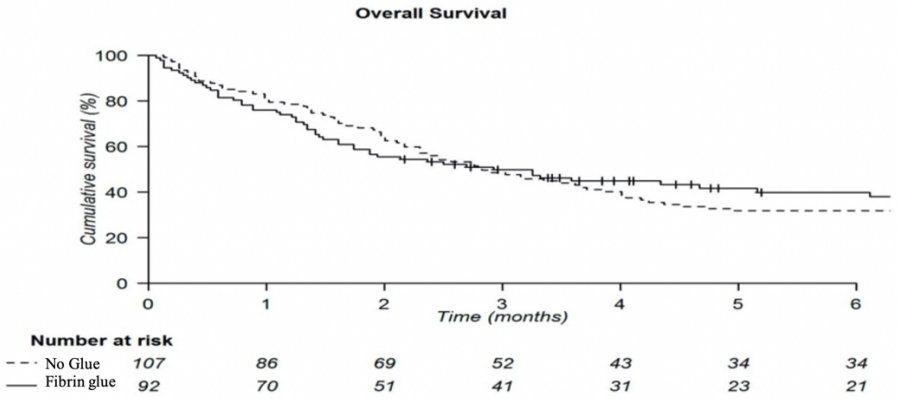

Figure 3 : Overall survival

4.5. Costs:

The cost of the procedure is low 165 €. Our study did not show any significant difference in length of hospital stay between the two arms (No Glue M = 9 D, 7-13 ; Fibrin Glue M = 9 D , 8-12 p =0,67) nor any difference in hospitalization costs (No Glue M = 9335€, 8373-25550, Fibrin Glue M = 9147€, 8181-13071 p =0,496) even if median is lower.

4.6. Adverse Effects :

Of note is the fact that, at no time during the study, were adverse effects linked to injection of fibrin Glue observed: no anaphylactic or anaphylactoid reactions, no medullary compression, no appearance of neurological (sensitive or motor) symptoms that could be attributed to fibrin glue injections or to the devices used.

5. Discussion

5.1. Preventive Effect on PDPH:

The results of this study clearly show a significant decrease in the incidence, duration, and intensity of PDPH with the prophylactic use of Fibrin Glue during the implantation procedure to treat CSF leakage induced by dural puncture. The initial rate of PDPH, in the group before the prophylactic use of the biological glue are slightly higher (32.7%) than a similar recent publication where a rate of 23% was reported (20) limited to the first 48 hours after the surgery. In our study, the assessment of PDPH was extended to one week following surgery because the symptoms often appear after getting up from the recumbent position, which often occurs later in the post-operative period in frail cancer patients. The large cohort of 199 patients over 2 years, provides sufficient power to perform data analysis despite its retrospective nature. Our results are also consistent with those found in a previous study (31). The needle diameter was proved to be the most important factor of fluid loss after CSF puncture, 6-fold greater with 22G than with 25G (32). The major advantage of this technique is its prophylactic nature in a procedure where using atraumatic and small diameter needles (10,33) is not an option, and the introducer is, of necessity, 16G thickness. Besides the Fibrin Glue application only patient age is a significant factor for PDPH occurrence.

5.2. Feasibility and safety:

Over one year, and with 4 different physicians, the procedure was achieved, even if it was sometimes challenging to find the path of the needle with the glue application canula, but it was always done in few minutes. This technique appears also reproductible with different

physicians as only 2 failures, were observed (2.04%) due to the inability of introducing the cannula into the needle path.

We were concerned about the final spread and location of the glue application, whether inside the CSF or in the epidural space or both. One patient did have an MRI for clinical care, early in the post-operative course and ten days after , and this reveal a distribution in epidural and intrathecal spaces (Figure 4). No adverse effects on spine was observed after fibrin glue injection despite imagery confirm intrathecal diffusion.

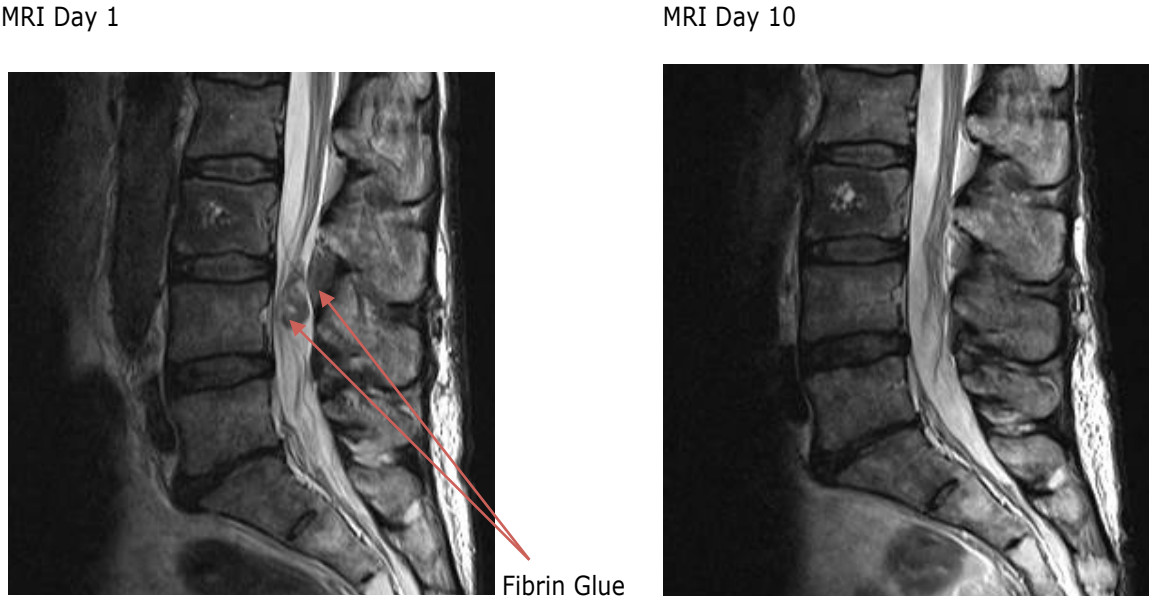

Figure 4 : MRI images confirming intrathecal diffusion

Furthermore, this technique appears safe. No adverse effects were observed, no allergic reaction and no neurological complication, which is not surprising since the glue is liquid and the limited volume avoids a compressive effect. In addition, fibrin Glue is absorbed, as shown in the imaging carried out ten days after the application (Figure 4). This avoids the risk of long-term complication.

However, we are aware of difference between US and Europe authorizations. The FDA does not clearly recommend fibrin glue for dura sealing use, so it is prohibited. Nevertheless, on

the other hand, in France the use of 40mg/ml concentrated Bupivacaine is prohibited intrathecally for potential cardiac toxicity risk by the National Medicament Security Agency even for cancer patients. This restriction seems unreasonable. By working to improve IDDS treatments with studies from both sides of the ocean, we contribute to develop the therapy.

The cost of the procedure is low: 165 € per patient. Even if we did not find a significant reduction in hospital stay and costs, the average reduction in hospitalization cost is equivalent to the fibrin glue cost. In addition, in our country drugs are not taken into account in the final bill for a hospitalization. The reduction for headache and nausea treatments should also be evaluated but we do not have these data for a cost evaluation. . Finally, In a retrospective study published in 2005(34), the author concluded that if dura Seal were to be used prophylactically for every procedure, and assuming a 4% leak rate post procedure a saving of $ 550 for every single neurosurgical procedure would be observed.

5.3. Limitation:

The main limitation of this study is its retrospective nature, with a risk of missing data, however data were well detailed on the electronic record. Additionally, the Lybecker score was applied retrospectively by the study physicians. In addition, this study is from a single center with a potential selection bias. Moreover, the procedure can indeed be improved. It is essential to find a more accurate technique to reach the epidural space. Another key point is to specify the optimal volume of fibrin glue required. Without prior data, we selected this volume based on the experiments conducted on animals. The strengths remain the large cohort of 199 patients and the fact that four different physicians performed the procedure decreasing potential for variability and bias.

6. Conclusion

Intrathecal drug delivery is an effective treatment for refractory cancer pain and is widely recommended. However, implantation presents risks of complications which are a barrier to the patients. Indeed, as improving the quality of life is one of the main indications and complications can delay that improvement especially when the life expectancy is short.

CSF leakage syndrome is a major concern, hard to manage after its occurrence, and likely to significantly alter patient's quality of life. The prevention is therefore an important goal, as, unlike in spinal anesthesia, using smaller needles is impossible. In this context, the prevention of PDPH by fibrin glue application seems to be a major innovation. This first evaluation is quite promising both in terms of efficacy and safety. Moreover, its moderate cost and reproducibility make it an affordable technique. Further prospective trials will be required to confirm these results.

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DOUILLARD Thomas

Prévention des maux de tête post-ponction lombaire après l'implantation d'un système d'administration intrathécale de médicaments grâce à l'application préventive de colle de fibrine : étude rétrospective.

RÉSUMÉ

Contexte : Les fuites de liquide céphalo-rachidien (LCR) peuvent entraîner un « syndrome post ponction lombaire » (SPPL). Cet effet secondaire est fréquemment observé après mise en place d'un cathéter intra-thécal (CIT). Ce syndrome post ponction lombaire affecte la qualité de vie des patients et peut entraîner d'autres complications. La colle biologique est utilisée pour traiter les fuites de LCR. Nous avons développé une méthode pour réduire l'incidence de ces céphalées par l'administration de colle biologique pendant la mise en place du CIT.
Objectif : le critère de jugement principal était l'incidence du SPPL après implantation du CIT avec ou sans colle biologique.
Design : Etude monocentrique rétrospective comparant 2 cohortes de patient bénéficiant de la mise en place d'une pompe intrathécale avec ou sans colle biologique sur 2 périodes successives.
Méthode : Introduction de la colle au contact de la zone de ponction lors de la mise en place du cathéter, après retrait de l'aiguille de ponction.
Résultat : 107 patients sans colle biologique (C-) et 92 avec colle (C+). On note 2 échecs d'administration. L'application de colle entraîne une diminution significative de l'incidence du SPPL, de 32,7% dans le groupe C- à 10,92% (p <0,001) dans le groupe C+. En ce qui concerne la sévérité, dans le groupe C-, 37,1% des SPPL étaient légers, 34,3% modérés et 28,6% sévères. Dans le groupe C+, 80% des SPPL étaient légers, 20% modérés et 0% sévère. La durée des symptômes était statistiquement plus courte dans le groupe C+ (maximum de 3 jours, contre 15 jours dans le groupe C-). En analyse univariée, l'application de colle et l'âge étaient significatifs pour prévenir le SPPL. En analyse multivariée, seul l'application de colle était significative (OR = 0.26 p = 0.0008). Nous n'avons pas observé d'effets secondaires liés à l'application de colle biologique.
Limite : Le caractère rétrospectif et monocentrique entraine un risque de biais de sélection et d'effet centre.
Conclusion : L'utilisation de colle biologique est prometteuse en terme d'efficacité et de sécurité pour limiter les syndromes post ponction lombaire après mise en place d'un cathéter intra-thécal par voie chirurgicale. Son coût modéré et sa reproductibilité en font une technique abordable et efficace.

Mots-clés : Syndrome post ponction lombaire, fuite de liquide cérébro-spinal, thérapie intra-thécale, colle biologique, douleur oncologique, soin palliatif

Preventing Post Dural Puncture Headache after Intrathecal Drug Delivery System Implantation through Preventive Fibrin glue Application : a retrospective study

ABSTRACT

Background: Cerebrospinal Fluid (CSF) leakage resulting in Post Dural Puncture Headache (PDPH) is a frequent Adverse Effect (AE) observed after Intrathecal Drug Delivery System (IDDS) implantation. CSF leakage symptoms negatively affect patient quality of life and can result in additional complications. Fibrin Glue was used to treat CSF leakage syndrome. We developed a procedure to reduce the incidence of PDPH by prevent CSF leakage with the use of Fibrin Glue during surgery.
Objectives: The main outcome criterion for this study was the incidence of Post Dural Puncture Headache syndrome after IDDS implantation with or without preventive Fibrin Glue application during the procedure.
Study design: We designed a mono-centric retrospective cohort study, in order to compare the incidence of PDPH due to CSF leakage syndrome after lumbar puncture in patients implanted with an intrathecal pump, with or without preventive Fibrin Glue application during the procedure.
Methods: The study compared two patient cohorts over two successive periods. Fibrin glue was injected into the introducer needle puncture pathway, after placement of the catheter, immediately following needle removal.
Results: The No-Glue group numbered 107, while the Glue group numbered 92. Two application failures were observed (2.04%). Fibrin Glue application results in a significant decrease in Post Dural Puncture Headache (PDPH) incidence, from 32.7% in the No-Glue group to 10.92 % (p<0,001) in the Glue group. As regards severity, in the No-Glue group, 37.1% of PDPH Syndromes were Mild, 34.3% were Moderate, and 28.6% were Severe. In the Fibrin Glue group, 80% of PDPH Syndromes were Mild, and 20% were Moderate. No Severe PDPH were reported after Fibrin Glue application. Duration of symptoms was also statistically shorter in the Fibrin Glue group (maximum of 3 days, versus 15 days in the No Glue group). In a univariate analysis, preventive Fibrin Glue application and age are significant to prevent PDPH. In multivariate analysis only Fibrin Glue application is statistically significant (OR = 0.26 p = 0.0008). No adverse effects linked to Fibrin Glue were observed.
Limitations: The main limitation of this study is its retrospective nature. In addition, this study is from a single center with a potential selection bias and a center effect.
Conclusion: The novel use of Fibrin Glue is promising in terms of its effect on PDPH and its safety profile. Its moderate cost and reproducibility make it an affordable and efficient technique.

Keywords : Fibrin Glue Post-dural Puncture Headache, Intrathecal Therapy, Surgical Outcome, Cancer Pain, Palliative Care, Hospice

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