Clinical Radiology 74 (2019) 166.e9–166.e13

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Effectiveness of premedication protocol using intravenous fentanyl to reduce pain associated with femoral artery closure device placement

A.I. Qureshi [a], M.A. Saleem [a,b,*], N. Naseem [a], S.S. Wallery [c]

[a] Zeenat Qureshi Stroke Institute, St Cloud, MN, USA
[b] Mercyhealth Janesville, WI, USA
[c] University of Illinois and Mercyhealth Rockford, IL, USA

ARTICLE INFORMATION

Article history:
Received 3 August 2018
Accepted 26 October 2018

AIM: To test the effectiveness of a premedication protocol using intravenous bolus of 100 μg fentanyl to reduce pain associated with femoral artery closure device placement for neuroendovascular procedures.

MATERIALS AND METHODS: The severity of pain associated with femoral artery closure device placement was analysed using a numerical rating scale score ranging from 0 (no pain) to 10 (most severe pain) in two cohorts of consecutive adult patients (n=118), those who were (n=64) or were not (n=54) treated with premedication protocol. The primary endpoints were the proportion of patients with excellent (score ≤1) and failed pain control (score ≥8). Stepwise logistic regression analysis was performed to identify the effect of premedication on pain control after adjustment for potential confounders.

RESULTS: The median numerical pain rating score at femoral artery closure device placement was significantly lower in patients treated with premedication protocol compared with those who underwent closure without premedication (1 versus 5, p<0.001). There was a significantly higher rate of excellent (56.2% versus 14.8%, p<0.001) and good (68.7% versus 31.2%, p<0.001) pain control at closure device placement among patients treated with premedication protocol. None of the patients treated with premedication protocol reported failed pain control compared with 33.4% of those who underwent closure device placement without premedication. In the multivariate analysis, treatment with the premedication protocol was significantly associated with an increased rate of excellent pain control (odds ratio 2.3; 95% confidence interval 1.9–3.1).

CONCLUSION: Premedication with intravenous fentanyl injection prior to femoral artery closure device placement can reduce the intensity of pain associated with closure.

Introduction

Occurrence of pain during femoral artery catheterisation using modified Seldinger's technique is well recognised.[1] Local infiltration of lidocaine in the subcutaneous tissue

* Guarantor and correspondent: M. A. Saleem, 849 Kellogg Avenue, Janesville, WI 53545, USA. Tel.: +1 (630) 550 9344.
E-mail address: akmamsaleem@gmail.com (M.A. Saleem).

https://doi.org/10.1016/j.crad.2018.10.016
0009-9260/

overlying the artery is the current standard analgesia to reduce local pain during the insertion process.[1] Previous studies have advocated the use of local spray or topical anaesthetic creams as adjunct to local lidocaine infiltration to reduce the pain during arterial catheterisation predominantly in the paediatric population.[2–4] Vascular closure devices are increasingly being used for femoral arteriotomy closure after diagnostic and interventional angiography and are associated with shortened time to haemostasis, ambulation, and discharge compared with manual compression.[5–7] Although the occurrence of pain during insertion and deployment of closure devices is known and even considered as the most painful portion of the procedure,[8,9] protocols for pain control have not been evaluated or incorporated into practice. The present study reports the results of a prospective protocol to determine the effectiveness of premedication with intravenous fentanyl injection prior to femoral artery closure in adult patients undergoing neuro-endovascular procedures.

Materials and methods

A prospective registry was maintained to determine the effectiveness of EMLA cream (lidocaine 2.5% and prilocaine 2.5%) prior to femoral artery catheterisation and the protocol for data collection was reviewed and approved by the local institutional review board as previously reported.[10] EMLA cream was applied at least 60 minutes prior to the procedure on the skin overlying the palpable femoral artery under an occlusive dressing over a 5×5 cm area as part of the routine care of all patients who underwent non-emergent neuro-endovascular procedures in the awake state at a single institution. Local infiltration of 10 ml lidocaine (1% solution) using a 10 ml sterile syringe was performed prior to insertion of a thin-wall needle (19 G) via percutaneous entry. Each patient received an intravenous bolus of 1 mg midazolam and 50 μg fentanyl prior to needle insertion. Due to the occurrence of pain during closure device placement, patients were asked about pain during femoral artery closure device placement which was recorded for the last 54 consecutive patients. Subsequently, all patients who underwent femoral artery closure device placement received a single intravenous bolus of 100 μg fentanyl approximately 3–5 minutes prior to femoral artery closure device placement. Femoral artery access site catheterisation was performed using a modified Seldinger's technique and closure was achieved using the Angio-Seal Vascular Closure Device (Terumo, Leuven Belgium) by one physician (A.I.Q.).

Intravenous fentanyl bolus in doses of 0.5–1 μg/kg has been used for pain control for minimally invasive procedures and in the postoperative period.[11,12] Higher doses of intravenous fentanyl (1–3 μg/kg) have been used in patients undergoing endovascular abdominal aortic aneurysm repair without any adverse effects on cardiovascular stability or level of consciousness.[13] Intravenous fentanyl as a 50 μg bolus was used for pain control during initial femoral artery access site catheterisation. A higher bolus dose of 100 μg of intravenous fentanyl was used prior to femoral artery closure device placement because the existing data suggested that the magnitude of pain was greater at closure compared with initial catheterisation.[9]

Data collected

The body habitus overflying the femoral arterial pulsation was classified as previously described[10]: (1) pubic symphysis and iliac crest bone protuberance visualised on gross examination of femoral region; (2) pubic symphysis and iliac crest bone protuberances are not seen, but easily palpable; (3) pubic symphysis and iliac crest bone protuberance is not seen, but palpable with considerable difficulty; (4) the abdominal layers fold over the femoral region. Body mass index was graded as underweight, <17 kg/m^2; normal, 17–24.9 kg/m^2; grade 1 overweight (overweight), 25–29.9 kg/m^2; grade 2 overweight (obesity), 30–39.9 kg/m^2; grade 3 overweight (severe or morbid obesity), ≥ 40 kg/m^2. Ease of cannulation was graded as: insertion at first attempt (grade 1), a number of minor adjustments needed (grade 2), a second attempt required (grade 3), or failure of 2 or more attempts (grade 4).[14] Previous history of femoral artery catheterisations and technical details regarding femoral artery catheterisation (introducer sheath used) and duration of procedures were collected. The severity of pain at femoral artery catheterisation and closure of the femoral artery catheterisation site were classified using a numerical rating scale score ranging from 0 (no pain) to 10 (most severe pain ever experienced) as reported from each patient. All inquiries were made by one investigator (A.I.Q.) to maintain consistency. A complete record of intravenous analgesics and sedatives used during the procedure was maintained.

Statistical considerations

The two cohorts of consecutive patients based on whether or not they were treated with premedication protocol prior to femoral artery closure device placement were compared. Formal sample size calculations were not performed as part of the study. The two groups were compared regarding demographic characteristics (age and gender), body habitus, body mass index, vascular risk factors such as diabetes mellitus, previous history of femoral artery catheterisations, ease of cannulation, duration of procedures and size of the largest femoral arterial sheath used. Categorical variables were expressed as frequency and compared using the chi-square test. Multiple comparisons were adjusted for using Bonferroni correction. The median numerical pain rating score for pain at femoral artery closure device placement was compared between the two groups using Mann–Whitney *U*-test. The proportion of patients with good (numerical rating scale score of 3 or less) and excellent (numerical rating scale score of 1 or less) pain control, and failed pain control (numerical rating scale score of 8 or more) were compared between the two groups. Logistic regression analyses were performed to identify predictors of excellent pain control and failed pain control (SPSS Version 20, IBM, Armonk, NY, USA). Age strata,

gender, obesity grades, ease of cannulation grade, body habitus grade, previous femoral arterial procedure, presence of diabetes mellitus, and pain at insertion were entered as potential predictors. A p-value of <0.05 was considered significant in the final model.

Results

A total of 118 patients (mean age ± SD, 56.2±17.4) were included in the analysis. The body habitus was graded as 1 (n=24), 2 (n=39), 3 (n=28), and 4 (n=27). The ease of cannulation was rated as grade 1 (n=74), 2 (n=29), 3 (n=11), and 4 (n=4). The mean (±SD) and median numerical rating scale scores at femoral artery catheterisation were 2.3±2.7 and 1 (range 0–10), respectively. The mean (±SD) and median numerical rating scale scores at femoral artery closure device placement were 5.2±4.3 and 5 (range 0–10), respectively.

A total of 54 patients underwent femoral artery closure device placement prior to and 64 patients underwent closure after the premedication protocol was implemented. There were no differences in mean age or proportion of men between the two groups of patients (see Table 1). The distribution of patients within strata of obesity and body habitus grades was similar. There was a trend towards higher rate of previous femoral artery catheterisation among patients treated with premedication protocol. The procedure time was significantly longer among patients treated with premedication protocol. There appeared to be lower rates of excellent pain control at initial femoral artery catheterisation among patients treated with the premedication protocol.

The median numerical pain rating score for pain at femoral artery closure device placement was significantly lower in patients treated with the premedication protocol compared with those who underwent closure without premedication (1 versus 4, $p<0.001$). There was a significantly higher rate of excellent (56.2% versus 14.8%, $p<0.001$) and good (68.7% versus 31.2%, $p<0.001$) pain control at femoral artery closure device placement among patients treated with the premedication protocol compared with those who did not receive premedication. None of the patients among those treated with the premedication protocol reported failed pain control compared with 33.4% of those who underwent femoral artery closure device placement without premedication.

In the multivariate analysis, treatment with the premedication protocol was significantly associated with increased rate of excellent pain control at femoral artery closure device placement (odds ratio [OR] 2.3; 95% confidence interval [CI] 1.9–3.1). Previous femoral arterial procedure [OR 3.2; 95% CI 1.7–5.2] and grade 4 body habitus [OR 1.7; 95% CI 1.1–2.7] independently predicted failed pain control at femoral artery closure device placement.

Table 1
Demographic and clinical characteristics of patients who were and were not treated with premedication protocol prior to femoral artery closure device placement.

N	Received premedication	Did not receive premedication	p-Value
	64	54	
Age strata			0.79
<45 years	8 (12.5)	11 (20.4)	
45–64 years	25 (39.1)	21 (38.9)	
65–79 years	23 (35.9)	18 (33.3)	
≥80 years	8 (12.5)	4 (7.4)	
Gender			0.34
Men	28 (43.8)	19 (35.2)	
Women	36 (56.3)	35 (64.8)	
Obesity			0.46
Underweight	2 (3.1)	3 (5.6)	
Normal	11 (17.2)	15 (27.8)	
Obesity (type I)	28 (43.7)	20 (37)	
Obesity (type II)	18 (28.2)	13 (24)	
Morbid obesity (type III)	5 (7.8)	3 (5.6)	
Body habitus			0.67
Grade 1	13 (20.3)	11 (20.4)	
Grade 2	24 (37.5)	15 (27.8)	
Grade 3	14 (21.9)	14 (25.9)	
Grade 4	13 (20.3)	14 (25.9)	
Ease of cannulation			0.89
Grade 1	41 (64.1)	33 (61.2)	
Grade 2	16 (25.1)	13 (24.1)	
Grade 3	6 (9.3)	5 (9.2)	
Grade 4	1 (1.5)	3 (5.5)	
Introducer sheath			0.67
5 F	56 (87.5)	41 (75.9)	
Others	8 (12.5)	13 (24.1)	
Previous femoral arterial procedure	23 (35.9)	11 (20.4)	0.07
Diabetes mellitus	18 (28.2)	19 (35.2)	0.43
Duration of procedure in minutes (mean ± standard deviation)	129 ± 67	113 ± 54	0.047
Pain at femoral artery catheterization			0.041
Excellent control	27 (42.2)	33 (61.1)	
Yes	37 (57.8)	21 (38.9)	
No			0.12
Good control	37 (57.8)	39 (72.2)	
Yes	27 (42.2)	15 (27.8)	
No			0.65
Failed control	2 (3.1)	3 (5.5)	
Yes	62 (96.9)	51 (94.5)	
No			
Pain at femoral artery closure device placement			
Excellent control			<0.001
Yes	36 (56.2)	8 (14.8)	
No	28 (43.8)	46 (85.2)	
Good control			<0.001
Yes	44 (68.7)	17 (31.2)	
No	20 (31.3)	37 (68.8)	
Failed control			-
Yes	0	18 (33.4)	
No	64 (100)	36 (66.6)	

Discussion

A significantly higher rate of excellent pain control was observed in the present cohort of patients treated with premedication protocol using intravenous fentanyl injection prior to femoral artery closure device placement compared with those in whom premedication was not used. None of the patients treated with intravenous fentanyl injection prior to femoral artery closure device placement

reported failed pain control compared with 33.4% of those in whom premedication was not used. The median numerical pain rating score for pain was significantly lower at femoral artery closure device placement in patients treated with premedication protocol. The two groups of patients were well matched regarding body mass index, body habitus, and ease of femoral artery catheterisation. Patients treated with intravenous fentanyl injection prior to femoral artery closure device placement had more unfavourable characteristics, such as lower rates of excellent pain control at initial femoral artery catheterisation and previous femoral artery catheterisations. Fentanyl citrate was used, which is a rapidly acting synthetic narcotic with a high affinity for the μ-opioid receptor. A dose of 100 μg (2 ml) is approximately equivalent in analgesic activity to 10 mg morphine or 75 mg meperidine.[11] The onset of action is almost immediate and usual duration of action of the analgesic effect is 30–60 minutes after a single intravenous dose of up to 100 μg (0.1 mg).[15] Fentanyl produces less cardiovascular depression and nausea and vomiting than either meperidine or morphine[16,17] and has been used in radiological special procedures for almost four decades.[18]

Certain aspects of study design should be considered prior to interpretation of the results. Formal sample size calculations were not performed. If the rate of excellent pain control is 15% in the control group, the power to detect absolute difference of 10%, 20%, and 30% with premedication protocol is 26.4%, 70.4%, and 95.3% with current sample size.[19] Therefore, the sample size may not be able to detect smaller differences in effect. Data regarding body habitus overflying the femoral arterial pulsation and ease of initial cannulation were collected as both may be related to subsequent technical difficulty in insertion and deployment of closure device. Each person's pain perception and severity threshold vary, and having a measure of pain perception prior to the administration of fentanyl and closure device deployment may be helpful to adjust for inter-patient variability in pain perception. Information regarding procedure time was provided because longer procedures and associated immobility may increase the anxiety and stress for patients. The above-mentioned variables also provide procedural variables that may assist in generalisability of the results. Patients were asked to rate pain experienced during femoral artery closure device deployment after 10–15 minutes following administration of intravenous fentanyl. Patients were able to respond to the query and provide a number on numerical rating scale in each case; however, pain control may partly be due to sedative rather than the analgesic effect of fentanyl.

The pain at femoral artery closure device placement is related to additional femoral region procedures as part of closure.[20] The Angio-Seal Vascular Closure Device (Terumo) consists of a delivery device with a biodegradable anchor and a collagen plug tethered together by a suture. A 70-cm, J-tipped guide wire (0.035-inch for 6 F and 0.038-inch for 8 F) distal tip, which is placed into the femoral artery through the existing femoral arterial sheath. The existing femoral arterial sheath is removed leaving the 70-cm, J-tipped guide wire in the femoral artery. Manual compression is applied on the arteriotomy site to avoid bleeding around the wire, which can be painful. An arteriotomy locator and introducer sheath are advanced over a 70-cm, J-tipped guide wire through the skin and subcutaneous tissue overlying the artery, which can be painful particularly if the previous sheath was smaller (5 F). The arteriotomy locator and J wire are removed leaving the introducer sheath just distal to the arteriotomy site. The delivery device is advanced through the introducer sheath until the anchor is deployed. The delivery device and the introducer sheath are withdrawn together until the anchor is up against the arterial wall. Collagen is also deployed an attached to suture through a tamper tube. The tamper tube is pushed down the suture while maintaining constant retraction on the suture. The arterial wall is subject to the anchor being retracted against the inner wall while the collagen plug being pressed down on the outer wall of the artery (see Fig 1). These last parts of the procedure appear to be very painful for the patient. The arterial wall is innervated by perivascular nerves, which are predominantly sympathetic and extend into the tunica adventitia and outer media ending in nerve terminal varicosities containing various neurotransmitters.[21, 22] The pain response is secondary to local activation of these autonomic nerves by mechanical compression.

Previous studies have compared the pain associated with various closure devices and manual compression. A previous study compared the pain associated with deployment between Mynx M5 (AccessClosure, Mountain View, California, USA) and the Angio-Seal Evolution.[9] A total of 64 patients were randomised on a 1:1 basis to either closure device. Both pain at closure and pain increase from baseline to closure were significantly higher in the patients randomised to Angio-Seal. A total of 88% and 34% of patients randomised to Angio-Seal and Mynx, respectively, reported closure as the most painful portion of the procedure. Another study[8] evaluated pain and discomfort score immediately after the closure procedure, at time for mobilisation, at discharge, and after 14 days among 1,001 patients randomised in a randomised, single centre comparison of FemoSeal (St Jude Medical Systems, St Paul, MN, USA) closure device versus manual compression after femoral arterial catheterisation. The pain score was assessed immediately after the closure procedure, at time for mobilisation, at discharge and after 14 days. The pain score during the procedure was significantly higher in patients who received the FemoSeal closure device, but no

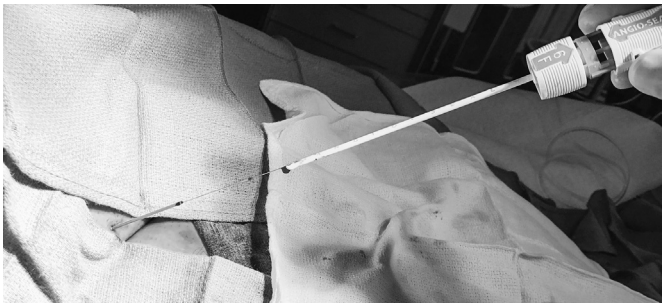

Figure 1 Deployment of the Angio-Seal device.

differences in pain and discomfort were detected at discharge and after 14 days.

The present study demonstrates that a premedication protocol using intravenous fentanyl injection prior to femoral artery closure device placement can reduce the intensity of pain associated with closure and may be considered to improve patient comfort and tolerance to neuro-endovascular procedures.

Conflict of interest

The authors declare no conflict of interest.

References

1. Spiliopoulos S, Katsanos K, Diamantopoulos A, *et al*. Does ultrasound-guided lidocaine injection improve local anaesthesia before femoral artery catheterization? *Clin Radiol* 2011;**66**(5):449–55.
2. Joly LM, Spaulding C, Monchi M, *et al*. Topical lidocaine–prilocaine cream (EMLA) versus local infiltration anesthesia for radial artery cannulation. *Anesth Analg* 1998;**87**(2):403–6.
3. Rusch D, Koch T, Seel F, *et al*. Vapocoolant spray versus lidocaine infiltration for radial artery cannulation: a prospective, randomized, controlled clinical trial. *J Cardiothorac Vasc Anesth* 2017;**31**(1):77–83.
4. Pirat A, Karaaslan P, Candan S, *et al*. Topical EMLA cream versus prilocaine infiltration for pediatric cardiac catheterization. *J Cardiothorac Vasc Anesth* 2005;**19**(5):642–5.
5. Schulz-Schupke S, Helde S, Gewalt S, *et al*. Comparison of vascular closure devices vs manual compression after femoral artery puncture: the ISAR-CLOSURE randomized clinical trial. *JAMA* 2014;**312**(19):1981–7.
6. Cox T, Blair L, Huntington C, *et al*. Systematic review of randomized controlled trials comparing manual compression to vascular closure devices for diagnostic and therapeutic arterial procedures. *Surg Technol Int* 2015;**27**:32–44.
7. Mankerious N, Mayer K, Gewalt SM, *et al*. Comparison of the FemoSeal vascular closure device with manual compression after femoral artery puncture—post-hoc analysis of a large-scale, randomized clinical trial. *J Invasive Cardiol* 2018.
8. Sindberg B, Schou M, Hansen L, *et al*. Pain and discomfort in closure of femoral access coronary angiography. The CLOSuredEvices used in everyday practice (CLOSE-UP) pain sub study. *Eur J Cardiovasc Nurs* 2014;**13**(3):221–6.
9. Fargen KM, Hoh BL, Mocco J. A prospective randomized single-blind trial of patient comfort following vessel closure: extravascular synthetic sealant closure provides less pain than a self-tightening suture vascular compression device. *J Neurointerventional Surg* 2011;**3**(3):219–23.
10. Qureshi AI, Saleem MA, Naseem N, *et al*. Effectiveness of topical lidocaine-prilocaine cream for pain control during femoral artery catheterization in adult patients: A prospective study. *J Vasc Interv Neurol* 2018;**10**(1):60–4.
11. Ogurlu M, Kucuk M, Bilgin F, *et al*. Comparison of bolus remifentanil-propofol versus bolus fentanyl–propofol for dilatation and sharp curettage. *Clin Exp Obstet Gynecol* 2010;**37**(3):209–12.
12. Choi Y-J, Park S-W, Kwon H-J, *et al*. Efficacy of early intravenous bolus oxycodone or fentanyl in emergence from general anaesthesia and postoperative analgesia following laparoscopic cholecystectomy: a randomized trial. *J Int Med Res* 2015;**43**(6):809–18.
13. Bonfreschi V, Giuliani E, Malagnino FC, *et al*. Analgesia during abdominal aortic aneurysm endovascular repair: remifentanil vs. fentanyl–midazolam — a randomized controlled trial. *Eur J Anaesthesiol* 2009;**26**(9):782–7.
14. Browne J, Awad I, Plant R, *et al*. Topical amethocaine (Ametop) is superior to EMLA for intravenous cannulation. Eutectic mixture of local anesthetics. *Can J Anaesth* 1999;**46**(11):1014–8.
15. U.S. Food and Drug Administration. *Fentanyl citrate injection, USP*. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/016619s034lbl.pdf. [Accessed 7 May 2018].
16. Rayburn WF, Smith CV, Parriott JE, *et al*. Randomized comparison of meperidine and fentanyl during labor. *Obstet Gynecol* 1989;**74**(4):604–6.
17. Rayburn W, Rathke A, Leuschen MP, *et al*. Fentanyl citrate analgesia during labor. *Am J Obstet Gynecol* 1989;**161**(1):202–6.
18. Miller DL, Wall RT. Fentanyl and diazepam for analgesia and sedation during radiologic special procedures. *Radiology* 1987;**162**(1 Pt 1):195–8.
19. *ClinCalc. Post-hoc power calculator*. 2018. Available at: http://clincalc.com/stats/Power.aspx. [Accessed 23 September 2018].
20. Rilling WS, Dicker M. Arterial puncture closure using a collagen plug, I. (Angio-Seal). *Tech Vasc Interv Radiol* 2003;**6**(2):76–81.
21. Chistiakov DA, Ashwell KW, Orekhov AN, *et al*. Innervation of the arterial wall and its modification in atherosclerosis. *Auton Neurosci* 2015;**193**:7–11.
22. Sheng Y, Zhu L. The crosstalk between autonomic nervous system and blood vessels. *Int J Physiol Pathophysiol Pharmacol* 2018;**10**(1):17–28.