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REVIEW

Pain Management Protocols During Uterine Fibroid Embolisation: A Systematic Review of the Evidence

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Abstract

Background Uterine fibroid embolisation (UFE) is an effective treatment for fibroids. There are varying analgesia protocols published to control procedure associated pain. We aimed to assess what protocols are most effective in controlling post-procedural pain.

Materials and Methods A systematic review of the Embase and Medline databases was conducted according to PRISMA guidelines. Studies regarding analgesia protocols post-uterine fibroid embolisation with Visual Analogue Scale or Numerical Rating Scale pain scores were included. The mean maximal pain scores of patients post-procedure were evaluated. ANOVA and *t* tests were performed.

Results We identified 26 studies (total 3353 patients), with a mean procedural success rate of $> 87\%$. We stratified protocols into four groups. Mean pain scores were: opioids ± NSAIDs ± acetaminophen (4.84, SD = 1.56); opioids ± NSAIDs ± acetaminophen + nerve block (4.7, SD = 1.37); opioids ± NSAIDs ± acetaminophen + intrauterine artery drug administration (4.09, SD = 0.60); and opioids ± NSAIDs ± acetaminophen + other (5.30, SD = 1.13) without significant difference between groups ($p = 0.71$). Similarly, there was no difference ($p = 0.057$) between groups for time to discharge or side effects.

Conclusions There is no evidence to suggest that there is any superiority of one protocol above another in the published literature. Appropriate use of opioids ± NSAIDs ± acetaminophen alone appears to be sufficient to control pain post-UFE. However, due to large heterogeneity of the literature no firm conclusions can be reached, and further research is warranted.

Level of Evidence Level 1, Systematic review.

Keywords Uterine artery embolisation · Fibroids · Pain management

Introduction

Uterine fibroid artery embolisation (UFE) has become a standard treatment option in the management of patients with symptomatic uterine fibroids. There is a growing volume of literature demonstrating the effectiveness and safety of this technique [1–3], while many regulatory bodies around the world have included UFE in their recommendations [3]. The minimally invasive nature of this method, the preservation of the uterus and the very short recovery time make this treatment option particularly attractive.

One of the main issues around UFE treatment is the significant amount of post-operative pain [1–3] that sometimes occurs within the first 24 h and can be challenging to manage and may lead to delayed discharged and increased use of opioids. Currently, this is probably the main reason why most patients undergoing UFE have to

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have an overnight stay at the hospital with the associated increase in cost and patient inconvenience. Various protocols have been described in the literature with the majority being based on the use of opioids and non-steroidal anti-inflammatories (NSAIDs). The introduction of patient control analgesia (PCA) has been a significant step in improving post-embolisation pain symptoms, and more recently invasive methods such as nerve blocks or intrauterine artery drug administration have also been suggested as a more effective way of improving post-operative pain and shortening recovery time and hospital stay [21–28].

The aim of this systematic review is to compare the effectiveness of the various invasive and non-invasive pain management protocols for the management of the post-UFE pain.

Methods

We conducted a systematic review according to the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. We performed a literature research in PubMed and Scopus databases by using the following key terms: "uterine artery embolization" OR "fibroid embolization" AND "pain management" OR "pain control" OR "analgesia". Two investigators (AE and AS) independently performed the literature search, study selection, data extraction and quality evaluation. In case of disagreement, there was a consensus meeting between all authors. Our literature search was concluded on 1 March 2019. Otherwise, there was no time limitation to our search.

Study Selection

Studies were included in the analysis if they met the following criteria: (1) human patients with uterine fibroids, (2) patients who were treated via UFE, (3) studies with over 10 patients, (4) studies reporting data on pain scores using Numerical Rating Scores (NRS), Visual Analogue Score (VAS) or equivalent pain scoring system on a scale of 0–10.

Data Extraction

We extracted data about study design, number of patients, technical success of procedure, analgesic protocol, discharge day, complications and mean maximal pain score from 0 to 10. The mean maximal pain score stated in each individual study was used in the statistical analyses.

Study Quality Assessment

The quality of the studies included was assessed using the Methodological Index for Non-Randomised Studies (MINORS) except in the case for randomised studies, in which case the Coleman Methodology Score was employed.

Statistical Analysis

The mean and standard deviation were calculated and compared with the ANOVA and t test statistical methods with fixed analyses using SPSS v24. Comparisons between the analgesic protocols were performed with the threshold of significance at $p < 0.05$.

Results

Quality analysis of the randomised controlled trials in this systematic review was conducted using the modified Coleman Methodology Score giving the studies scores of 62–84 out of a maximum score of 100. Observational and comparative studies were both assessed with the Methodological Index for Non-Randomised Studies (MINORS). Observational studies obtained scored ranging between 9 and 12 out of a maximum of 16, whereas comparative studies scored 16–18 with a maximum possible score of 24. Data in these studies were distributed homogeneously (Levene statistic $F(3,24) = 0.757$, $p = 0.529$).

In each of the four groups of protocols, some studies utilised patient-controlled analgesia (PCA) to manage pain. We conducted independent t test analyses in these four groups which show that the use of PCA does not cause any significant difference in pain scores in our sample studies. PCA opioid ± NSAID ± acetaminophen vs opioid ± NSAID ± acetaminophen $p = 0.80$. PCA opioid ± NSAID ± acetaminophen + nerve block versus opioid ± NSAID ± acetaminophen + nerve block $p = 0.405$. PCA opioid ± NSAID ± acetaminophen + intrauterine drug administration vs opioid ± NSAID ± acetaminophen + intrauterine drug administration $p = 0.344$. For the group involving opioid ± NSAID ± acetaminophen and other, PCA versus non PCA had a p value of 0.028; however, since there are only three studies in this comparison, this test may not be representative. Hence, we decided to not separate protocols which involved PCA from those that did not in further analyses.

We identified 129 studies, of which 26 met all inclusion criteria (21 prospective and 5 retrospective) with a total of 3353 patients and a technical success rate exceeding 87% (Fig. 1) (Tables 1, 2). Thirteen of these studies were

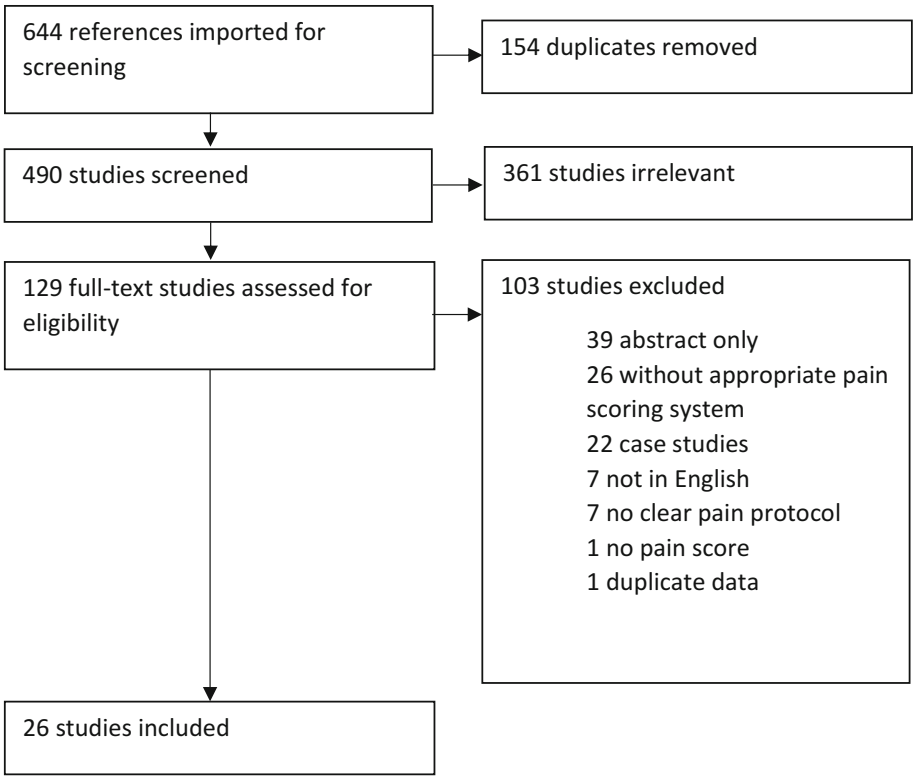

Fig. 1 Flowchart

randomised. The majority of these studies ($N = 17$) employed an analgesic protocol, which included opioids ± NSAIDs ± acetaminophen. The remaining studies used protocols including opioids ± NSAIDs ± acetaminophen + nerve block ($N = 4$); opioids ± NSAIDs ± acetaminophen + intrauterine arterial drug administration ($N = 3$); or opioids ± NSAIDs ± acetaminophen + other ($N = 2$) (Table 1). Due to high heterogeneity in different time periods that the pain score was recorded, we decided to conduct our analyses using the maximum mean pain score.

In the opioids ± NSAIDs ± acetaminophen group, 2632 patients were recruited from 16 studies with a mean reported UFE technical success rate of 97.9% (range 87.5–100%) [4–15, 17–20]. The mean maximal pain score for all patients treated with this analgesic protocol was 4.84 (range 2.5–8, SD 1.55). The mean proportion of patients discharged on the same day of the procedure was 26.9%, with 46.5% discharged after one day and 26.6% of patients requiring more than one night admission post-UFE. Complications were reported in 12 studies in this group ($N = 1313$). The most common complications in the group were vomiting (2.1%), fatigue (1.7%), anorexia (1.7%), vaginal bleeding (1.4%), prolapse/expulsed fibroid (0.5%), amenorrhoea (0.6%), groin haematoma (0.3%) and fever (0.3%).

The four papers which utilised opioids ± NSAIDs ± acetaminophen + nerve block as their analgesic method recruited a total of 313 patients and had a technical success rate for procedure of 99.5% (range 98.6–100%) [21–24]. Average maximal pain score for patients who were on this analgesia protocol was 4.77 (range 3–6, SD 0.72). An average of 93.94% of patients were discharged on the day of procedure. Complications in this group were reported in three studies ($N = 174$). The most common reported complications were minor neurological symptoms, such as back pain and mild sensory loss (4.5%), fever (4%), amenorrhoea (2.8%), groin haematoma (1.7%) and prolapse/expulsion of fibroid (1.1%).

In three studies, opioids ± NSAIDs ± acetaminophen + intrauterine artery administration of drugs was utilised, with a total of 238 patients recruited. The technical success rate in this group was 99.05% (range 98.1–100%) and a mean maximal pain score of 4.09 (range 3.5–4.71, SD 0.60) [26–28]. 97.39% of patients were discharged on the same day of procedure, and 2.61% of patients were discharged after 1 day. No patients had to remain in hospital for more than 1 day. Complications were only reported by one study ($N = 160$) in this group and included contrast reaction (0.6%) and fibroid expulsion (3%).

Three studies used opioids ± NSAIDs ± acetaminophen with other types of drugs (steroids, ketamine, or α_2 adrenergic receptor agonists) in their analgesic protocols [16, 29, 30]. This group of studies contained 170 patients who had a mean maximal pain score of 5.3 (range 4–6, SD 1.13) with a 100% technical success rate. No patients were discharged on the same day of the procedure,

Table 1 Clinical studies regarding uterine fibroid embolisation using VAS/NRS scores for post-procedural pain

Author	Study design	Pain protocol	Number of patients	Technical success (%)	Mean Maximal Pain Score[a]	Day of discharge (%)			MINORS/ Modified Coleman Methodology Score	Reported complications
						Same day	Next day	≥ 2 Days post-procedure		
Bilhim et al. [4]	Observational study, retrospective	Opioids ± NSAIDs ± acetaminophen	900	ND	2.5	ND	ND	ND	10/16	ND
Lipszyc et al. [5]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen	19	ND	8	ND	ND	ND	70/100	ND
Pron et al. [14]	Observational study, prospective	Opioids ± NSAIDs ± acetaminophen	555	97	7	2.19	79.93	17.88	11/16	Pain ($N = 32$), seizure, HTN and respiratory depression ($N = 3$), HTN ($N = 2$), fever ($N = 2$), aspiration pneumonia ($N = 1$), pulmonary oedema ($N = 1$), UTI ($N = 1$), prolapsed fibroids ($N = 1$)
Cunningham et al. [15]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen	16	87.50	5	25.00	62.50	12.50	73/100	ND
Pisco et al. [17]	Observational study, retrospective	Opioids ± NSAIDs ± acetaminophen	234	ND	2.5	100.00	0.00	0.00	9/16	Pain, nausea, vomiting ($N = 26$), fatigue ($N = 23$), anorexia ($N = 21$), vaginal bleeding ($N = 18$), abdominal swelling ($N = 26$), small inguinal hernia ($N = 5$), fibroid expulsion ($N = 4$), amenorrhoea ($N = 8$)
Ruuskanen et al. [18]	Observational study, prospective	Opioids ± NSAIDs ± acetaminophen	62	100	5.1	ND	ND	ND	10/16	Groin haematoma ($N = 3$)
Konstantatos et al. [19]	Randomised control study	Opioids ± NSAIDs ± acetaminophen	39	ND	3.2	0	11	89	77/100	ND
Roth et al. [20]	Observational study, prospective	Opioids ± NSAIDs ± acetaminophen	81	ND	4.8	0.00	100.00	0.00	12/16	ND
Siskin et al. [6]	Observational study, prospective	Opioids ± NSAIDs ± acetaminophen	49	98	5.7	95.20	4.80	0.00	12/16	Prolonged fever ($N = 1$), prolonged intractable pain ($N = 1$)
Ryu et al. [7]	Comparative study, retrospective	Opioids ± NSAIDs ± acetaminophen	72	100	5.07	ND	ND	ND	18/24	ND
Katsumori et al. [8]	Comparative study, retrospective	Opioids ± NSAIDs ± acetaminophen	101	100	5.9	0.00	0.00	100.00	17/24	ND
Chiu et al. [9]	Observational study, prospective	Opioids ± NSAIDs ± acetaminophen	12	100	6	0.00	0.00	100.00	10/16	No complications

Table 1 continued

Author	Study design	Pain protocol	Number of patients	Technical success (%)	Mean Maximal Pain Score[a]	Day of discharge (%)			MINORS/ Modified Coleman Methodology Score	Reported complications
						Same day	Next day	≥ 2 Days post-procedure		
Kim et al. [10]	Comparative study, prospective	Opioids ± NSAIDs ± acetaminophen	200	ND	4.5	0.00	100.00	0.00	18/24	No minor complications due to PCA, no major complications
Spies et al. [11]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen	100	99	4.89	0.00	100.00	0.00	82/100	Urinary retention ($N = 1$), herpes exacerbation ($N = 1$), minor haematoma ($N = 1$), migraine ($N = 1$), rash/hives ($N = 10$), fibroid passage ($N = 2$), PE ($N = 1$), pain ($N = 2$).
Rasuli et al. [12]	Observational study, retrospective	Opioids ± NSAIDs ± acetaminophen	101	ND	3.7	100.00	0.00	0.00	10/16	Pain ($N = 6$), nausea and vomiting ($N = 2$), fever ($N = 1$), urinary retention, constipation, vaginal discharge
Barnard et al. [13][b]	Randomised control study, prospective, comparative study, prospective	Opioids ± NSAIDs ± acetaminophen	91	100	2.7	0.00	100.00	0.00	78/100 17/24	ND
Rasuli et al. [24]	Observational study, prospective	Opioids, NSAIDs ± acetaminophen + nerve block	139	ND	5.7	100.00	0.00	0.00	16/24	ND
Pisco et al. [22]	Comparative study, prospective	Opioids, NSAIDs ± acetaminophen + nerve block	70	98.60	3	100.00	0.00	0.00	17/24	Fibroid expulsion ($N = 2$) readmission due to pain ($N = 1$), fever ($N = 7$), abdominal swelling ($N = 7$), vaginal bleeding ($N = 6$), constipation ($N = 4$), inguinal haematoma ($N = 3$)
Freire et al.[23]	Randomised control study, prospective	Opioids, NSAIDs ± acetaminophen + nerve block	60	100	6	ND	ND	ND	62/100	No major complications
Yoon et al. [21]	Randomised control study, prospective	Opioids, NSAIDs ± acetaminophen + nerve block	44	100	4.4	81.82	ND	ND	79/100	Back pain ($N = 6$), difficulty advancing 21 gauge SHNB needle ($N = 1$), tachycardia ($N = 1$), blood aspiration before injection of block agent ($N = 1$), sensation of heat in foot ($N = 1$), heaviness of foot ($N = 1$)
Keyoung et al. [26]	Randomised control study, prospective	Opioids, NSAIDs ± acetaminophen + intra-UA drug administration	18	ND	3.5	ND	ND	ND	70/100	ND
Noel-Lamy et al. [27]	Randomised control study, prospective	Opioids, NSAIDs ± acetaminophen + intra-UA drug administration	60	100	3.66	ND	ND	ND	84/100	ND

Table 1 continued

Author	Study design	Pain protocol	Number of patients	Technical success (%)	Mean Maximal Pain Score[a]	Day of discharge (%)			MINORS/Modified Coleman Methodology Score	Reported complications
						Same day	Next day	≥ 2 Days post-procedure		
Billhim et al. [28]	Randomised control study, prospective	Opioids, NSAIDs ± acetaminophen + intra-UA drug administration	160	98.10	4.71	97.39	2.61	0.00	68/100	Contrast reaction (N = 1), fibroid expulsion (N = 6), amenorrhoea (N = 5)
Kim et al. [29]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen + other	50	ND	4	ND	ND	ND	76/100	Pain, fever and vaginal discharge(N = 1)
Jensen et al. [16]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen + other	56	100	5.8	0.00	100.00	0.00	72/100	ND
Kim et al. [30]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen + other	64	ND	6	0.00	100.00	0.00	67/100	ND

NSAIDs non-steroidal anti-inflammatory drugs, *%* percentage, *intra-UA* intrauterine artery, *SHNB* superior hypogastric nerve block, *HTN* hypertension, *UTI* urinary tract infection, *ND* no data, *MINORS* Methodological Index for Non-Randomised Studies (0–16 for observational studies, 0–24 for comparative studies)

[a]Due to high variability in the time of reporting pain scores, the highest mean pain score reported was used in analysis

[b]This study had a randomised control trial and a comprehensive cohort design in parallel

98.3% were discharged on the next day, and 1.7% of patients had a hospital stay of over 1 day. One study (N = 50) reported an individual patient who experienced complications of pain fever and vaginal discharge in this group.

Comparison of the mean maximal pain scores across the four different groups using ANOVA analysis shows no significant difference between the effectiveness of the various analgesic protocols (p = 0.71) and hence no demonstrable benefit of additional and more invasive analgesia to the opioid ± NSAIDs ± acetaminophen protocol. A two-tailed Welch's t test comparing the mean percentage of the patients who were discharged on the same day of procedure in the opioids ± NSAIDs ± acetaminophen group of studies (mean 24.8%, SD 42.5%) against studies which used opioids ± NSAIDs ± acetaminophen + nerve block, opioids ± NSAIDs ± acetaminophen + intrauterine artery administration of drugs, or opioids ± NSAIDs ± acetaminophen + other (mean 63.2%, SD 49.4%) also showed no statistical difference (p = 0.139, CI − 92.3 to 15.5%) (Table 3).

Further analysis was conducted on the opioid ± NSAID ± acetaminophen group. We further stratified this group into two smaller groups: those using fentanyl/remifentanil and those not. We conducted t test analysis on protocols which included fentanyl or remifentanil (mean 5.87, SD 1.25) and which protocols that did not (mean 3.94, SD 1.30). This showed that there is a significant reduction in mean pain score in protocols that do not use fentanyl or remifentanil compared to studies that do (p = 0.01) (Table 4). Subgroup analyses on the other protocol groups would not be very meaningful due to the small number of studies in the other groups.

Discussion

Since the first described UFE procedure by Ravina et al. in 1995, UFE [2] has gained widespread international popularity for the treatment of symptomatic fibroids. Clinical trials demonstrated marked reduction of pain and hospital stay compared to hysterectomy [25]. Although uterine artery embolisation is a minimally invasive procedure, there is usually significant post-procedural pain. Multiple factors have been suspected causing the variation to the pain responses including fibroid volume, race, type of particles used, demographic and cultural pain threshold [2, 25]. Many analgesia protocols have been adopted; however, there is still no consensus regarding which protocol is the most cost-effective.

This systematic review aimed to assess whether there is improved pain control when using different analgesia protocols and in particular invasive versus non-invasive

Table 2 Analgesic protocol and embolisation agents of included clinical studies

Author	Study design	Pain protocol	Drugs in protocol				Embolisation agent
			Pre-procedural	Peri-procedural	Post-procedural	Discharge	
Bilhim et al. [4]	Observational study, retrospective	Opioids ± NSAIDs ± acetaminophen	Oral naproxen 1000 mg IV metamizol 2 g IV tramadol 100 mg IV piroxicam 20 mg	IV ketorolac 60 mg IA ketoprofen 100 mg	IV acetaminophen 1 g IV metamizol 2 g IV ketorolac 30 mg IV piroxicam 20 mg IV tramadol 100 mg	Oral naproxen 500 mg BD Oral tramadol with acetaminophen 37.5/325 mg PRN Oral codeine with acetaminophen 30/500 mg PRN	PVA particles
Lipszyc et al. [5]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen		PCA remifentanil 2ug/ml or PCA morphine 2 mg/ml	PCA remifentanil 2ug/ml or PCA morphine 2 mg/ml PLUS IV acetaminophen 2 g QDS IV diclofenac 75 mg BD		ND
Pron et al. [14]	Observational study, prospective	Opioids ± NSAIDs ± acetaminophen	Oral/IV ketorolac 30 mg/IM ibuprofen 30 mg/rectal indomethacin 50 mg/	Fentanyl/ meperidine/morphine	PCA morphine 1–1.5 mg bolus Oral ibuprofen 800 mg, then 600 mg 4 h	Oral ibuprofen 600 mg QDS Codeine/oxycodone with acetaminophen	355–500 μm PVA particles Gelfoam Coils
Cunningham et al. [15]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen	IV morphine 2 mg IV ketorolac 60 mg	Morphine as per need Fentanyl as per need Meperidine as per need		Ibuprofen 600/800 mg Naproxen 550 mg Hydrocodone with acetaminophen 5/500 mg/ propoxyphene with acetaminophen 50/325 mg/ oxycodone with acetaminophen 10/325 mg/codeine with acetaminophen 30/300 mg	ND

Table 2 continued

Author	Study design	Pain protocol	Drugs in protocol				Embolisation agent
			Pre-procedural	Peri-procedural	Post-procedural	Discharge	
Pisco et al. [17]	Observational study, retrospective	Opioids ± NSAIDs ± acetaminophen	Oral naproxen 1000 mg IV metamizole 2 g IV tramadol 100 mg IV piroxicam 20 mg	IV ketorolac 60 mg	IV acetaminophen 1 g IV metamizol 2 g IV ketorolac 30 mg IV piroxicam 20 mg IV tramadol 100 mg		300–500 µm PVA particles 500–700 µm PVA particles
Ruuskanen et al. [18]	Observational study, prospective	Opioids ± NSAIDs ± acetaminophen			IV ibuprofen and oxycodone 0.5 mg/10 kg or IM ibuprofen and oxycodone 1 mg/10 kg Oral oxycodone 10 mg PLUS PCA analgesia	Oral ibuprofen 800 mg TDS or Oral acetaminophen 1 g TDS	550–700 µm microspheres
Konstantatos et al. [19]	Randomised control study	Opioids ± NSAIDs ± acetaminophen	Oral oxycodone 20 mg Oral acetaminophen 1.5 g Oral piroxicam 20 mg	PCA morphine 1 mg bolus	PCA morphine 1 mg bolus Oral oxycodone 5 mg		500–700 µm PVA foam particles
Roth et al. [20]	Observational study, prospective	Opioids ± NSAIDs ± acetaminophen			PCA morphine 1 mg bolus Ketorolac	Oral ketorolac Oral hydrmorphine Oral oxycodone with acetaminophen	500–710 µm PVA particles
Siskin et al. [6]	Observational study, prospective	Opioids ± NSAIDs ± acetaminophen		IV fentanyl 50 µg IV ketorolac 60 mg	IV meperidine 75 mg IV ketorolac 30 mg Oral hydroxycodone and acetaminophen 15 mg	Oral meperidine 100 mg QDS Hydrocodone Oral ketorolac 10 mg QDS Oral ibuprofen 400 mg QDS	350–500 µm PVA particles Gelfoam
Ryu et al. [7]	Comparative study, retrospective	Opioids ± NSAIDs ± acetaminophen			PCA morphine		Emboshperes PVA particles

Table 2 continued

Author	Study design	Pain protocol	Drugs in protocol				Embolisation agent
			Pre-procedural	Peri-procedural	Post-procedural	Discharge	
Katsumori et al. [8]	Comparative study, retrospective	Opioids ± NSAIDs ± acetaminophen			Oral diclofenac 50 mg IM morphine 10 mg IV morphine 1.25-3.75 mg PCA morphine 0.5 mg bolus Oral loxoprofen 60 mg	Oral naproxen 600 mg TDS	Gelatin sponge 500–700 μm tris-acryl gelatin microspheres 700–900 μm tris-acryl gelatin microspheres
Chiu et al. [9]	Observational study, prospective	Opioids ± NSAIDs ± acetaminophen		IV fentanyl 0.05–0.1 mg Rectal indomethacin 100 mg	IM pithidine		300–500 μm PVA particles
Kim et al. [10]	Comparative study, prospective	Opioids ± NSAIDs ± acetaminophen		IV fentanyl 50/100ug IV ketorolac 60 mg	PCA morphine 1 mg bolus OR PCA fentanyl 25 ug bolus PLUS IV ketorolac 30 mg		500–700 μm microspheres
Spies et al. [11]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen			PCA morphine/ fentanyl/ hydrocodone		355–500 μm PVA particles 500–710 μm PVA particles 500–700 μm microspheres 700–900 μm microspheres
Rasuli et al. [12]	Observational study, retrospective	Opioids ± NSAIDs ± acetaminophen	Rectal diclofenac 100 mg	IV morphine 2–5 mg	Oral morphine 30 mg IV morphine 2 mg PRN IV demerol 25–75 mg	Oral morphine 30 mg BD Oral morphine 10 mg QDS Rectal diclofenac 100 mg OD	300–500 μm PVA particles

Table 2 continued

Author	Study design	Pain protocol	Drugs in protocol				Embolisation agent
			Pre-procedural	Peri-procedural	Post-procedural	Discharge	
Barnard et al. [13][a]	Randomised control study, prospective Comparative study, prospective	Opioids ± NSAIDs ± acetaminophen				Oral oxycodone 5 mg Oral ibuprofen 600 mg Acetaminophen PRN	500–700 µm tris-acryl gelatin microspheres 700–900 µm tris-acryl gelatin microspheres
Rasuli et al. [24]	Observational study, prospective	Opioid ± NSAIDs ± acetaminophen + nerve block	Rectal indomethacin 100 mg IV fentanyl 50 mg PRN or Rectal naprosyn 500 mg IV morphine 5–10 mg IV fentanyl PRN	Intra-thecal bupivicaine 20 ml 0.25%	IV fentanyl 25 ug PRN or oral morphine 30 mg IV morphine 2 mg PRN	Oral morphine 10 mg QDS Rectal indomethacin 100 mg BD or oral morphine 30 mg BD Moral morphine 10 mg QDS Rectal naprosyn 500 mg OD	400–600 µm PVA particles 300–500 µm PVA particles 500–700 µm PVA particles
Pisco et al. [22]	Comparative study, prospective	Opioid ± NSAIDs ± acetaminophen + nerve block	Oral diclofenac 50 mg	IV piroxicam 20 mg IV metamizole 3/4 g IV tramadol 150/200 mg IA ketoprofen 100 mg Ketorolac 45/60 mg Acetaminophen 500 mg	Oral tramadol 37.5 mg Oral acetaminophen 325 mg IV tramadol 100 mg	Diclofenac 50 mg TDS Tramadol with acetaminophen 37.5/325 mg PRN Codeine with acetaminophen 30/500 mg	300–500 µm PVA particles 500–700 µm PVA particles
Freire et al. [23]	Randomised control study, prospective	Opioid ± NSAIDs ± acetaminophen + nerve block	Oral oxycodone 20 mg	Intra-thecal bupivicaine 15 mg Intra-thecal morphine 200 µg	IV ketoprofen 100 mg IV metamizole 2 g PCA morphine 2 mg bolus		500–700 µm microspheres 700–900 µm microspheres

Table 2 continued

Author	Study design	Pain protocol	Drugs in protocol				Embolisation agent
			Pre-procedural	Peri-procedural	Post-procedural	Discharge	
Yoon et al. [21]	Randomised control study, prospective	Opioid ± NSAIDs ± acetaminophen + nerve block		Intra-thecal lidocaine 3 ml 1% Intra-thecal ropivacaine 20 ml 0.5% IV fentanyl	IV fentanyl Oral oxycodone/ hydromorphine/ meperidine	Oral naproxen 500 mg BD Codeine with acetaminophen 30 mg QDS/ Tramadol with acetaminophen 37.5 mg QDS	500–710 µm PVA particles
Keyoung et al. [26]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen + intra-UA drug administration		IA lidocaine 200 mg Fentanyl IM ketorolac 30 mg IV ketorolac 30 mg	PCA morphine 0.5–2 mg bolus IV ketorolac 30 mg Acetaminophen Oral hydromorphine 2 mg Oral ketorolac 10 mg Oxycodone with acetaminophen	Oral ketorolac 10 mg Oral hydromorphine 2 mg PRN Oral oxycodone with Acetaminophen 5/325 mg PRN Oral ibuprofen PRN	500–710 µm PVA particles
Noel-Lamy et al. [27]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen + intra-UA drug administration	Oral acetaminophen 1000 mg Oral ibuprofen 400 mg Oral oxycodone 10 mg	Fentanyl Intra-thecal lidocaine 200 mg	Oral ibuprofen 400 mg Oral acetaminophen 1000 mg Oral oxycodone 10 mg IV hydromorphine 0.5–1 mg	Oral oxycodone with acetaminophen 2.5/ 325 mg	355–500 µm PVA particles
Bilhim et al. [28]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen + intra-UA drug administration	Oral naproxen 1000 mg IV metamizol 2 g IV tramadol 100 mg IV piroxicam 20 mg	IV ketorolac 60 mg IA ketoprofen 100 mg	IV acetaminophen 1 g IV metamizol 2 g IV ketorolac 30 mg IV piroxicam 20 mg Oral tramadol 37.5 mg Oral acetaminophen 325 mg IV tramadol 100 mg	Oral naproxen 500 mg Oral tramadol plus acetaminophen 37.5/ 325 mg PRN/ Oral codeine plus paracetamol 30/500 mg PRN	350–500 µm PVA particles 500–700 µm PVA particles 700–900 µm PVA particles

Table 2 continued

Author	Study design	Pain protocol	Drugs in protocol				Embolisation agent
			Pre-procedural	Peri-procedural	Post-procedural	Discharge	
Kim et al. [29]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen + other	IV dexmedetomidine 2ug/ml		PCA fentanyl 20 ug bolus PCA ketorolac Oral tramadol with acetaminophen 75/650 mg		250–355 µm PVA particles 355–500 µm PVA particles 500–700 µm PVA particles
Jensen et al. [16]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen + other	Oral acetaminophen 1 g Oral diclofenac 100 mg		PCA morphine 2 mg/ml or PCA morphine 2 mg/ml PCA ketamine 2 mg/ml PLUS Acetaminophen 1 g QDS Diclofenac 50 mg TDS	Oral naproxen 500 mg BD Oral tramadol plus acetaminophen 37.5/325 mg PRN Oral codeine plus paracetamol 30/500 mg PRN	355–500 µm PVA particles
Kim et al. [30]	Randomised control study, prospective	Opioids ± NSAIDs ± acetaminophen + other	Dexamethasone 10 mg		PCA fentanyl 20 µg bolus Oral tramadol with acetaminophen 75/650 mg		355–500 µm PVA particles 500–700 µm PVA particles

NSAIDs non-steroidal anti-inflammatory drugs, *%* percentage, *intra-UA* intrauterine artery, *ND* no data, *PRN* pro re nata, *mg* milligrams, *ug* micrograms, *PVA* polyvinyl alcohol

[a]This study had a randomised control trial and a comprehensive cohort design in parallel

Table 3 Comparison between groups of analgesic protocols

Protocol	Number of studies	Number of patients	Technical success (%)	Proportion of patients discharged same day (%)	Mean Maximal Pain Score[a]	Range	Standard deviation	*p* value
Opioids ± NSAIDs ± acetaminophen	16	2632	97.9	26.9	4.84	2.5–8.0	1.55	
Opioids ± NSAIDs ± acetaminophen + nerve block	4	313	99.5	93.9	4.77	3.0–6.0	0.72	
Opioids ± NSAIDs ± acetaminophen + intrauterine artery drug administration	3	238	99.05	97.4	4.09	3.5–4.71	0.60	
Opioids ± NSAIDs ± acetaminophen + other	3	170	100	0	5.3	4.0–6.0	1.13	$p = 0.71$

NSAIDs non-steroidal anti-inflammatory drugs, % percentage

[a]Due to high variability in the time of reporting pain scores, the highest mean pain score reported was used in analysis

Table 4 Comparing opioid ± NSAID ± acetaminophen protocols using fentanyl/remifentanil versus opioids ± NSAIDs ± acetaminophen protocols that do not use fentanyl/remifentanil

Protocol	Number of studies	Number of patients	Technical success (%)	Proportion of patients discharged same day (%)	Mean Maximal Pain Score[a]	Range	Standard deviation	*p* value
Opioids ± NSAIDs ± acetaminophen (fentanyl and remifentanil)	7	951	96.3	20.4	5.87	4.5–8.0	1.25	
Opioids ± NSAIDs ± acetaminophen (non fentanyl/remifentanil)	19	1681	100	33.3	4.13	2.5–5.9	1.36	$p = 0.017$

NSAIDs non-steroidal anti-inflammatory drugs, % percentage

[a]Due to high variability in the time of reporting pain scores, the highest mean pain score reported was used in analysis

pain protocols. Our study suggests that, despite opioids NSAIDs ± acetaminophen and intrauterine artery drug administration showing overall slightly better pain scores in comparison with the other treatment groups, this difference was not statistically significant. In addition, it was shown that there was no difference in terms of duration of hospital stay between the invasive and non-invasive protocols.

Noel-Lami et al. showed that although the use of intra-arterial lidocaine may improve pain for the first 4 h post-procedure, there was no significant effect in the pain levels in the subsequent 7–24 h. According to the authors, this was probably due to the short half-life of the local anaesthetic [27]. In addition to this, the investigators noted that mixing the lidocaine with the particles reduces the rate of complete infarction to 38.9% compared to 75% when the lidocaine was injected pre- or post-particle embolisation, which was reported to cause some vasospasm and increase the technical difficulty of the procedure [26].

Only three clinical trials were identified which looked at the benefits of adding steroids, ketamine, or alpha 2 adrenergic receptors blockers to the opioids protocol. These did not reveal any significant improvement in the average pain score, but due to the small number of studied patients no firm conclusions can be reached [16, 29, 30]. The available studies regarding the response to nerve block also showed no statistically significant benefit with significant variability between studies. Although some studies report that there is less opioids use when combined with a nerve block procedure [31], study variability has also been observed in nerve blocks performed for pain control in oncology patients [31] and this limits direct comparisons between many of these studies. It has also been suggested that the technical expertise and operator experience are possibly an important factor for the observed variability in outcomes [31]. The heterogeneity of the particles used is also another factor that limits the comparisons between the trials. Bilhim et al. [28], in their study with 160 patients, reported that there was significantly less pain when the procedure started with larger particles (500–700 m) compared to smaller particles (300–700 m).

In general, the complication profile of the studied pain control protocols does not appear to be significantly different between invasive and non-invasive pain protocol algorithms, with the only exception being the reported 4.5% incidence of back pain and mild sensory loss in the

nerve block group. The sensory loss reported resolved 4–6 h post-procedure with no long-term neurological deficit reported [21, 24]. Complication rate may reflect the experience of the operator as in most centres this is not a very common procedure. This complication, of course, could also significantly increase the cost of the procedure. Apart from this, all pain control regimes were safe, and complications reported in $< 3\%$ of the cases with no significant differences between treatment groups.

The post-procedural care can vary significantly between institutions. The data from the included studies did not reveal any significant difference in the hospital stay comparing the multiple pain protocols. One explanation for this can be the variation in the hospital admission policy of different institutions. Most institutions schedule the procedure as an overnight stay procedure rather than just an outpatient day case procedure. Where there is unplanned overnight admission, this has been mainly attributed to uncontrolled pain.

In the literature, there are limited reports of non-pharmaceutical analgesia alternatives in Pisco et al. [22] that studied the effect of percutaneous electrical nerve stimulation as a pain control method. A non-randomised clinical trial in 70 patients was performed reporting a reduced need for pharmaceutical analgesia when percutaneous electrical analgesia was utilised. All patients except one in each group were discharged from the hospital 4–8 h after UFE; the two who remained longer had severe pain. There were no significant differences in clinical outcomes, nor in uterine and leiomyoma volumes, at discharge and at 6 months ($p > 0.99$ and $p = 0.72$, respectively. Other methods such as hypnosis or regular acupuncture have also been suggested but never been clinically tested.

There are many limitations in this study. There is significant heterogeneity in the included study protocols with variations in the size of embolised fibroids, size of particles and pain score questionnaires used. In addition, the majority of the included studies had small sample sizes (especially in the invasive group) and heterogeneous patient groups and no long-term follow-up data had been recorded which is mirrored by their overall average MINOR scoring. The time period in which the pain scores were reported varied significantly, and due to this it was not possible to calculate a mean pain sore across all studies for any particular time period. We, instead, used data on the mean maximal pain score reported by the individual studies, regardless of time at which it occurred for our analyses. In addition, discharge times in most studies seem to have been predetermined according to institutional protocols and not so much based on the study protocol. Data about complications and readmissions across the studies included in the review were limited and incomplete across the different protocol groups. Hence, meaningful quantitative analyses of these data are not possible. Due to varying amount of follow-up and reported data in the studies, it was not possible to assess or do any meaningful quantitative analysis on complications, readmission or pain for time periods after the immediate post-procedural period. There is also an apparent lack of comparative studies between the various analgesia protocols limiting the comparisons between the various treatment protocols. No cost-effective analysis data were identified, and thus, we could not perform any analysis on the cost-effectiveness of invasive pain control protocols. Finally, there is always the risk of publication bias particularly when assessing non-randomised studies.

Conclusion

Currently, there is no evidence to suggest the superiority of any pain protocol over others. Randomised clinical trials focusing on hospitalisation time and utilising well-defined, internationally recognised pain scores are required to assess what is the optimal analgesic protocol and in particular whether there is any benefit from using invasive techniques for pain control post-UFE.

Compliance with Ethical Standards

Conflict of interest The authors declare they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent For this type of study, informed consent is not required.

Consent for Publication For this type of study, consent for publication is not required.

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