

## A Review of the Emerging Procedures of Analgesia in Patients with Acute Pain who Presented in the Emergency Medicine Department

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### Abstract

The existence of pain among patients is still one of the main causes of referring to the emergency departments. In this regard, special medical physicians of emergency staff should be responsible for treatment of the various levels of pain (acute to chronic) as well as management of pain induced from various kinds of illnesses or/and injuries. The treatment should be performed considering the harm limitation induced by analgesics. Inadequate pain treatment which is common in the emergency departments results in negative impacts on patient care. This exacerbated by improperly pain assessment and the possibility of using unsafe analgesics. As a result, emergency physicians always face a challenge in providing satisfactory analgesia while minimizing side effects either inside the emergency department or after hospital discharge. The present study aimed to recognize various methods of analgesia for emergency medicine physicians, provide them with different methods of pain relief and the way of use based on the patient's condition, and to improve their quality services. In this study, an extensive review of the scientific databases and search engines of PubMed, HubMed, MEDLINE, Science Direct, MedlinePlus, Scopus, and CINAHL were performed to achieve detailed publications on the pain management methods in the emergency situations. Afterward, the high-quality articles which were published from 2005 to 2019 on the issue of pain management methods in the emergency medicine department, were selected for further investigation. Although acute pains are mostly treated using non-opioids analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), the treatment of acute moderate to severe pains mostly requires opioid agents. Moreover, effective pain management in the emergency situations may be included the interventions through the application of Lidocaine intravenous, gabapentinoid agents, and different nonpharmacological analgesia agents. This study was performed with the aim of recognizing and evaluating the pros and cons of the available agents to provide the most appropriate methods for pain management in emergency medicine departments. Additional research is required on the safety and effectiveness of non-opioid treatment methods of analgesia within the emergency department.

**Keywords:** Pain, Emergency Medicine Service, Pain medicine Management, NSAIDs, Pain control.

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### Introduction

One of the main complaints of patients admitted to the medical health centers which account for nearly four-fifths of the being presented in the emergency departments (ED) is feeling pain. Various procedures of managing pain are known to be the major indicators of care quality in emergency department settings. On the other hand, all procedures of controlling pain could be influenced through various demographic factors of patients, the kind of illness, ability to express pain, pain express capability, persistent phobia of complications and the level of consciousness of physician (1,2). In the situation when patients are tolerating clinical and para-clinical operations or/and are waiting for test results the process of controlling pain should not be stopped. NSAIDs could be primarily applied to relieving the patients' pain effectively (3). These types of treatments must be capable of relieving various types of pain while having the lowest rate of drug interferes and adverse effects. The immediate treatment of pain in emergency department settings could be more satisfying for patients who attended to these places initially for treatment on their pain. On the other hand, the importance of the process of pain management in emergency department settings is to some extent that a global consensus is created for conducting more precise assessments on the matter of insufficient pain treatment in these settings (4,5).

The type of treatment in the emergency department ED is greatly influenced by the nature of pain presentation of patients in different levels of acute or chronic. Emergency physicians face unique challenges, e.g. opioid tolerance may be developed in patients who receive chronic analgesic treatment using opioid agents, leading to increased doses of opioids to

gain sufficient analgesia in them. Patients having breakthrough symptoms and suffering from chronic pain must visit their related physician. Anyway, patients who suffer from acute pain remain the responsibility of the emergency physician, and in some cases, there is no continuing care for patients (6,7).

Poor or insufficient pain management is a particular challenge in emergency medicine. The result of a Canadian study of seventy patients showed that only forty percent of patients with moderate-to-severe pains received analgesics when arriving at the ED, and less than 50% of patients with self-reported severe pains received an analgesic medication (8). According to a prospective study which is performed on twenty emergency departments in the Canada and United States (US), 74% of patients were discharged with remained moderate to severe pains, and only 60% of patients received analgesics for their pains (9).

In an emergency setting, clinicians meet challenges regarding the provision of effective treatment for acute pains. Although the professionals in the field of health care believe that patients' reports about the severity of their pain are accurate, both doctors and nurses usually underestimate the pain (10). Pain underestimation and inconsistent evaluation may be an important reason for insufficient treatment and has been reported to be especially common in female, geriatric, pediatric, and ethnic minority populations in the US (11). Moreover, due to the concerns regarding the drug safety (e.g. the potential of opioids to be abused) and the adverse effects related to NSAIDs, providers may restrict the prescribed agents for treatment of acute pain (12).

As a result, recognition of various methods of analgesia and pain management allows emergency medicine physicians (EMPs) to have a variety of options to reduce pain, and to be able to choose the best option according to the patient's condition, thus improving the quality of their services. The present study provides a qualitative review of recent research on ED pain practice, and clinical experiments about emerging approaches for pain treatment.

In this study, an extensive review of the scientific databases and search engines of PubMed, HubMed, MEDLINE, Science Direct, MedlinePlus, Scopus, and CINAHL were performed to achieve detailed publications on the pain management methods in the emergency situations. Afterward, the high-quality articles which were published from 2005 to 2019 on the issue of pain management methods in the emergency medicine department, were selected for further investigation. The search of the mentioned databases was lead to 274 articles. After the elimination of the articles with similar content, the most relevant records were selected to be precisely reviewed. PRISMA method was applied for searching, screening, elimination and selection of the most relevant records. PRISMA method is shown in figure 1 schematically.

### Recent procedures of pain relief

According to some recent research, injury or trauma pain is the cause of most pain reports in the emergency departments, and pain of traumatic etiology accounts for 30% of pain reports (Table 1). Non-traumatic diagnostic pain groups commonly included headache, abdominal pain, neck and back pain, upper respiratory infection and non-cardiac chest pain. The scores of pain intensity upon arrival varied from 4 to 10 with a median score of 8 (13). According to the previous researches, only half of patients experience pain reduction by 2 or over in a numeric rating scale (NRS) basis while the ED stay, and about 75% of patients remain with moderate to severe pain when discharging from ED (14).

Increasing evidence of opioid-related harms such as overdose and death has been revealed all over the world. Furthermore, the death of opioids overdose, and the overall sales of prescription opioids have been 4 fold since the first decade of the 20th century (15). It is hard to specify the correct contribution of ED opioid prescription in opioid-related harms within a certain region or country. However, previous studies showed that emergency medicine has a limited contribution. According to the US statistics, the contribution of emergency medicine in opioid prescriptions is less than five percent, which is lower than the contribution of surgeons, dentists, internists and even family physicians (8). Recently, some initiatives have been developed to enhance the inspection of those patients looking for treating their pain in the ED, such as programs with the ability to monitor the prescription drug. Accordingly, individual EDs and regulatory entities have established guidelines to reduce and systematize opioid prescribing (16). This resulted in a reduction of opioid-prescribing rates by nearly 11 percent in EDs up to now (8).

### Pain relief challenges

Opioids perform very well in the treatment of moderate to severe pains. In their study, Sebastian et al (17) reported that there were over 205 million cases of opioid prescriptions in the US, which indicates the broad use of opioids (17). Over the recent three decades, the number of opioid prescriptions have increased, especially for chronic pain. Monotherapy using opioids is not the optimal choice for patients who suffer from acute pain, because of the opioids potential to be abused, its side effects, and insufficient efficacy of opioids in comparison with other therapies in certain conditions (18, 19).

Nowadays, emergency care providers are reluctant to prescribe opioids due to the contemporary increase in opioids'

abuse, illegal diversion and its related morbidity and mortality (20). This could result in inadequate analgesia in patients who are mistaken with opioid-abuse individuals because of physician bias or similarity of behaviors between patients and drug-seeker individuals (21). Higher rates of misused opioids for pain relief objectives would result in greater mortality rates. Although some attempts have been performed to reduce the application of opioids, it is not clear if they lead to reduced mortality rates of an opioid overdose. Moreover, these attempts have not been pursued nationally. Prescription monitoring programs would modify the prescribing practices of emergency physicians for those patients who frequently refer to the ED for the purpose of pain medication (22).

Additionally, the use of opioids may cause hyperalgesia and tolerance, resulting in further complication of treatment through possibly intensified opioid use induced by the perception of inadequate pain treatment at the current doses. Although opioids perform well in some patients suffering from short-term acute pain, its use in ED patients does not always provide optimal consequences. On the other hand, the adverse side effects and the abuse potential of opioids indicate that caution is required when using opioids (23, 24). Similarly, acetaminophen, aspirin, and NSAIDs are also not appropriate for all patients, though they are typically well tolerated at doses used for acute pain treatments. Aspirin is an effective pain relief agent which is suitable in many pain conditions, even for severe pains. Administration of a single dose of aspirin equals to 600mg or 650 mg provided better pain relief in 40% of postoperative patients compared to those patients receiving placebo (25). However, aspirin at higher doses (2.4 to 3.9 g/day) is shown to be associated with tinnitus and gastrointestinal side effects. Acetaminophen is another efficient analgesic which can be used to mitigate less accurate pains, but it is not appropriate for all pain conditions (26).

According to the food and drug administration (FDA) federal agency, unintentional therapeutic misuse of acetaminophen has become a general concern contributing to hepatotoxicity (27). FDA recommended that acetaminophen acceptable dose within prescription drug productions should be reduced from 675 mg to 350 mg in each dose unit. FDA also recommended that prescription of combination therapies with more than 350 mg of acetaminophen should be discontinued by health care professionals. Furthermore, the FDA has restricted over-the-counter dosage of acetaminophen to 3 g per day in adults. NSAIDs are another frequently used analgesic agent which are very effective for relieving pains with inflammatory origin like musculoskeletal cancer pains (28, 29). The pain relief efficacy of NSAIDs is greater than opioids and a single dose of 400 mg ibuprofen could provide adequate pain relief. Anyway, the application of NSAIDs could cause cardiovascular and renal side effects and more intensive gastrointestinal disorders even in short periods of time. Thus, their use is more limited in patients with higher risk (30, 31) (Table 2).

### Management of pain at ED

There is firm evidence supporting the application of non-opioid and migraine-specific approaches for treating some common ED pain symptoms (such as benign headache). In spite of this well-established evidence, there has been a slow progression toward standardization of headache treatment in ED and prioritizing of non-opioid interventions (33). Despite a large body of evidence regarding its various side effects, opioids are still prescribed as a first treatment option for many ED patients with benign headaches in the United States. However, the application of opioid and migraine-specific therapies in ED settings has been reduced in most parts of the world (34, 35). Regional anesthesia is another promising approach administered by an emergency physician which is supported by many literature. Thanks to inclusive training

programs on emergency medicine in ultrasound, regional nerve blockade is being increasingly possible for many types of painful illnesses and injuries (36, 37). Appropriate pain management and optimal functional outcome require harmonious teamwork between anesthesiology and emergency medicine sections. For this purpose, emergency physicians play an important role in the establishment of this teamwork as well as in the delivery of regional anesthesia (38).

#### **Ketamine**

Ketamine has been applied for long times in ED for the management of patients with some kinds of acute pain and also as an induction agent for quick intubation. Ketamine in lower doses (0.1–0.4 mg/kg) has been used either as monotherapy or adjunctive therapy, with a more quickly prevalence than other non-opioid analgesics. Sub-dissociative dose ketamine has been identified to be effective and safe either as a single agent or as adjunctive therapy in combination with other opioids for the treatment of a variety of acute pains (39, 40). Although the association of ketamine with neuropsychiatric adverse effects is well known, its use in sub-dissociative doses has minor and short-time side effects. It is indicated that ketamine injection in a 15-min infusion period would result in fewer adverse effects (41, 42). Although sub-dissociative dose ketamine has been largely supported in the literature, patients should be informed about potential adverse effects of ketamine, and emergency physicians should avoid ketamine prescriptions for patients with psychiatric disorders. Anyway, when ketamine needs to be administered, it should be based on the established procedures and policies of the department (43-45).

#### **Morphine**

Due to its convenient accessibility in hospital systems, morphine is one of the most common opioid agents used in the treatment of patients with moderate to severe pain and those with extremity trauma (46). Currently, it has been recommended that the treatment of acute pain in ED performed by the use of bolus doses of morphine, following by gradual titration to the required analgesia (47). Morphine has a number of adverse side effects, such as respiratory depression, hypothermia, sedation, and nausea (48). Due to the side effects of morphine, most of the EMPs avoid using morphine at the initial bolus dose of 7 to 10 mg. There are two studies that show that intravenous morphine at 0.1 mg/kg cannot provide enough pain relief. However, most of the studies have shown that using morphine at standard doses, even for a long time, has no severe complications. In order to prevent its abuse, the preparation and administration of morphine has been controlled in hospitals, delaying its use (49). In their study, Virginie et al (50) revealed that administration of subcutaneous morphine can provide favorable analgesia for half an hour longer than its intravenous (IV) administration, however, they found no significant difference in analgesia provided by these two methods. Because of the fact that there is no need to IV access in subcutaneous administration, it can be a useful method in certain cases (50).

#### **Nitrous oxide**

The use of nitrous oxide as both analgesic and anxiolytic in pediatric ED patients dates back to a long time ago. A 60% nitrous oxide vapor can be administered for children who are undergoing the procedures such as laceration repair, venipuncture, incision and drainage of abscesses, and fracture reduction. The use of nitrous oxide has been restricted by factors such as scavenging equipment and proper ventilation requirement, and its abused potential (51). Nitrous oxide has had restricted application within adult patients in the ED. With regard to the current recommendations on the reduction of

opioid use in the ED, the use of nitrous oxide as a non-opioid agent is likely to be increased over time (52).

There are some other non-opioid analgesics with less robust evidence on their efficacy which have increasingly received attention. Recently, analgesic therapies such as IV lidocaine, gabapentinoids, trigger point injections, acupuncture, music therapy, and mind-body modalities have been developed for ED application (53). IV lidocaine has shown to be effective for neuropathic pain and central pain syndromes. It is also shown to have opioid-sparing impacts in post-operative conditions. When combined with morphine, intravenous lidocaine can be applied for the management of acute pain in ED patients with fewer adverse effects and quicker pain treatment and nausea compared to those received only morphine (54).

Given to the possible side effects of opioids, it is of great importance for knowing and employing other treatment techniques, such as physical interventions, patient-centered communication, and relaxation techniques. Moreover, the pain inciting factor(s) is often unknown to the emergency physician (55). Patients with pain usually exhibit co-morbid depression and anxiety, low self-efficacy, chemical coping behaviors, and catastrophizing ideation. We may regard such patients as a challenge to our professional career, and it may be difficult to maintain a positive therapeutic state in them (56).

#### **Ketorolac**

Ketorolac belongs to NSAIDs group which is sold with the brand name of Toradol, etc. It is used as an injectable painkiller in many developed countries such as the US and several European countries. Ketorolac is used due to its potent analgesic effect. The analgesic effect of ketorolac in acute pain management is similar to injectable opioids of pethidine and morphine (57, 58). The main advantages of ketorolac over the injectable opioids include the lack of dependence and respiratory depression and the long-lasting effect of relief. Additionally, ketorolac has synergistic effects with opioids, and the simultaneous use of injected ketorolac and opioids can decrease the necessary dose of opioids (59). ketorolac has the same efficacy with morphine in pain control, and simultaneous use of these two results in fewer side effects and reduction of the need for rescue therapy (60). In their study, Abdelwahab et al showed that although pethidine or ketorolac performed well in pain relief, the return time to normal life was shorter for ketorolac (61).

#### **Fentanyl**

Fentanyl is a synthetic fat-soluble opioid with the ability to remain up to 72 hours within the body, depending on the administration type (62). It is another type of opioid used in the ED which has a robust analgesic effect by 100 folds higher than morphine. IV fentanyl, compared with IV morphine, has a faster onset effect. Although IV fentanyl affects faster than IV morphine, it has shorter half-life about 30–60 minutes, thus requires more repeated doses to maintain pain control in a long time. Parental et al. found no significant difference in pain reduction and side effects between IV fentanyl and IV morphine (38, 63). Some studies reported that the application of fentanyl-based titration protocols resulted in improved analgesia in the ED with no increased side effects. As a result, it may be used as an alternative to IV morphine. Other studies have also reported that fentanyl is more preferred by patients than morphine, because of its fewer digestive tract complications such as constipation (64, 65).

Theoretically, IV administration of opioid should affect faster by almost 5 minutes than that of the intranasal (IN) method, due to the drug absorption mechanism. However, some studies reported no significant difference in the analgesic effect of IN fentanyl and IV morphine (66). Because of the bioavailability nature of IN fentanyl, it does not passing through the liver, thus

there are no adverse effects on the liver. The drug reaches a therapeutic serum level at approximately 2 minutes after administration. Moreover, because there is no need for IV access in IN fentanyl administration, it has superiority over IV morphine in certain cases (67).

### **Paracetamol**

Paracetamol which is also known as APAP and acetaminophen is commonly used for the treatment of fever and pain, especially for mild to moderate pain relief. It is a medication with less unwanted side effects than NSAIDs and opioids in therapeutic doses which can be used in the ED (68). According to the result of studies, the analgesic effects of injected paracetamol is comparable to that of injectable NSAIDs in the ED and is similar to that of morphine for treatment of some painful operations such as tooth extraction. Paracetamol is frequently used to pain relief after orthopedic surgeries (69). In their study, Samad et al found that paracetamol has a similar analgesic effect with injected morphine in renal colic treatment. Paracetamol can be an appropriate alternative of tramadol infusion for pain reduction in patients who are going to have heart surgery (70). Easy access and cheapness are other advantages of paracetamol over opiates. The simultaneous use of paracetamol and NSAIDs results in stronger analgesia in comparison with using NSAIDs alone (71).

### **Psychotherapy aspects**

Given to the ongoing crisis of opioid harm at the national level, emergency physicians should display their empathy when the treatment of patients with (without) the risk for opioid abuse. The empathy concept for patients who suffer from pain involves cognitive, affective and action elements. The ability of emergency physicians to display empathy and establishment of patient-oriented interactions are essential (72). An honest and sincere interaction between patient and physician is more likely to provide desired outcomes. Although this phenomenon has not been adequately studied in the ED setting, such empathic display may result in reduced analgesic requirements, especially for patients having high levels of anxiety. As a result, it should be incorporated into physician therapeutic armamentarium as an indivisible component (73). Those clinicians with the ability to successfully combine these skills into practice are more likely to perceive higher rates of patient satisfaction, better clinical outcomes, and enhanced treatment compliance. The higher self-management and self-efficacy of the patient by these practices, the more reduced healthcare costs, due to prevention of dispensable diagnostic imaging and inappropriate drug prescription (74). At last, empathy enhancement of emergency physicians with patients has the potential of reducing career burnout, lower medicolegal risk, and increased physician well-being (75).

### **Novel remedial alternatives**

Recent technological and methodological advancements can improve pain management through improved treatment allocation and proper pain assessment, without any increase in side effects or abuse potential (76). Visual Analogue Scale (VAS) is a measurement instrument that scores the various pain levels from zero (with no pain) to 10 (highest pain). The level of pain for each patient could be specified using a specific number within the range of 0-10. In order to define the cause and level of the pain, consistent and appropriate use of assessment tools is necessary. Moreover, the improvement of pain management standards requires progressive efforts (77). Accurate assessment of pain in patients with communicational disorders such as those with cognitive disabilities is especially challenging. In this regard, pain intensity evaluation by nurses

and controllability behavioral scale of various parts of the body are developed for nonverbal patients, which have been shown to produce comparable results with those obtained by the Numeric Rating Scale (78).

Anyway, patients admitted to the ED should be evaluated for pain level, mood, body movement, facial expression, and physiological signs. The result of studies has shown a high variability of responses to analgesic therapies and placebo, which suggest that genotypic differences of patients affect their response to therapy (79). Thanks to the availability of rapidly absorbed formulations and newer versions of NSAIDs such as drops, gels and patches, the faster and more effective treatment of acute pain has been possible. These newer formulations of NSAIDs include fewer active ingredients, which may result in an improved risk-benefit profile (Table 3) (80). The efficacy of topical formulations of NSAIDs in acute pain treatment has been illustrated. Also, they can result in higher drug concentrations within local tissue. The application of topical NSAIDs for musculoskeletal pain produces similar efficacy with oral NSAIDs but without the adverse effects seen in oral or IV-NSAIDs (81).

Rapidly absorbed formulations of NSAIDs may produce quick pain relief and result in lower side effects than traditional NSAIDs (Table 3) (83). The application of nasal spray agents is a simple and noninvasive modality which is able to provide rapid pain relief after the administration of NSAID or opioid with fewer systemic exposure. Diclofenac gel capsules developed by the use of finer-milled particles provide faster and more potent absorption features than those obtained by diclofenac potassium immediate-release tablets and may be prescribed as a suitable lower-dose alternative to traditional NSAID formulations (84). However, patients may perceive the new dosage forms as expensive. Neuropathic pain is one of the complicated forms of chronic pain which is commonly associated with tissue injury. Its underlying mechanism is not fully understood. Antidepressants, topical therapies, antiepileptic agents, and gamma-aminobutyric acid analogs can be applied for neuropathic pain sedation in certain conditions with effective consequences (85).

Pregabalin and gabapentin have an optional inhibitory effect over neurons that express voltage-gated calcium channels involving the subunit of alpha2-delta. These agents are regarded as a leading treatment choice for neuropathic pain management, alongside with serotonin, norepinephrine reuptake inhibitors, and tricyclic antidepressants (86). Although both of these agents have antihyperalgesic, anticonvulsant, and anxiolytic features, pregabalin displays better pharmacokinetic properties such as greater potency and dose-independent absorption, compared to gabapentin. Pregabalin has a similar structure with gabapentin and is developed as a modified lipophilic g-aminobutyric acid analog to transmit better across the blood-brain barrier (87). Gabapentin can be used for the treatment of central neuropathic pain, and is shown to have some efficacy in post-operative pain sedation with similar side effects to placebo. Inclusion of pregabalin in postoperative pain treatment may result improved analgesia in some patients, but it may be inefficient for other pain types (88). The most frequent adverse effects reported for pregabalin or gabapentin include somnolence, nausea, vomiting, and dizziness. Additionally, recent studies reported that pregabalin application may increase the risk of heart failure (89).

### **Pain management prospective**

Although ED pain management remains a challenge to emergency physicians, and despite the slow progression of our practice patterns, they could be regarded as encouraging trends for the future studies on new emergency medicine subdiscipline. There have recently been a number of

encouraging advancements in ED pain management. Today, emergency medicine skill training has been recognized as a field of pain medicine all over the world, and currently, there are a growing number of emergency physicians with good competence in this specialty (90). Emergency physicians do their best to attain more proficient certifications in their field of specialty. The recent advancements in recommendations for emergency medicine pain management are showing that there is a need for standardizing and role enhancement of pain medicine in the training of emergency medicine residency. However, further studies and education on acute and chronic pain management in the ED are required for further advancement in the field of emergency medicine and for proper management of pains (91).

### Conclusion

Non-opioids painkillers such as acetaminophen and NSAIDs are frequently used for acute pain treatment. However, opioid agents are usually applied for acute moderate-to-severe pain relief. Morphine, fentanyl, meperidine, and hydromorphone are the most common parenteral opioids used in acute pain treatment in the ED. Proper treatment of acute pain is one of the most important public health issues which has remained unmet. In response to this requirement, it is necessary to improve the effectiveness and risk profile of available treatments. Currently, there are some limiting factors in the selection of typical treatments for some patients, including limitations in pain assessment, mortality related to respiratory depression, the addiction potential of opioids, and dose-related NSAID side effects.

NSAIDs are another common group of therapeutic agents which although are less efficient in the first 10 minutes, have an equal effect to opioids during 20–30 minutes, and are well-tolerated in short-period use. NSAIDs perform better than morphine in controlling pain and result in fewer side effects and lower rescue treatment requirements. NSAIDs have anti-inflammatory effects due to their ability to inhibit prostaglandins which increase vessel permeability, reduce their dilatation, increase pelvic pressure and the urine collection system, and increase diuretic effects on the kidneys. They also decrease inflammation, swelling, and contractions of the ureter muscles. The application of NSAIDs is limited because of their renal and gastrointestinal adverse effects. However, their injectable version such as ketorolac has considerably reduced the rate of these complications.

In order to enhance the currently available treatments, several new approaches of pain therapy have been developed, including improvement of the efficacy and risk profile of existing drugs through their reformulation, application of psychoactive drugs which were not originally designed for analgesic purposes, development of combinatory therapies, and utilization of non-pharmacological therapies. Development of assessment and treatments approaches in accordance with the pain type and risk factors of each patient will result in more efficient pain management and can enhance the ability of emergency physicians to produce pain sedation in a more rapid and effective manner, and in the same time minimize the risks of adverse effects and abuse. Given the growing population and increasing general awareness of people as well as the advancement of medical knowledge, the selection and proper use of analgesic medications have become more important. In this regard, healthcare professionals face a great challenge, because the underlying cause of pain in patients is complicated, and usually accompanied by multiple comorbidities.

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### Conflict of Interest

The author has no conflicts of interest to declare.

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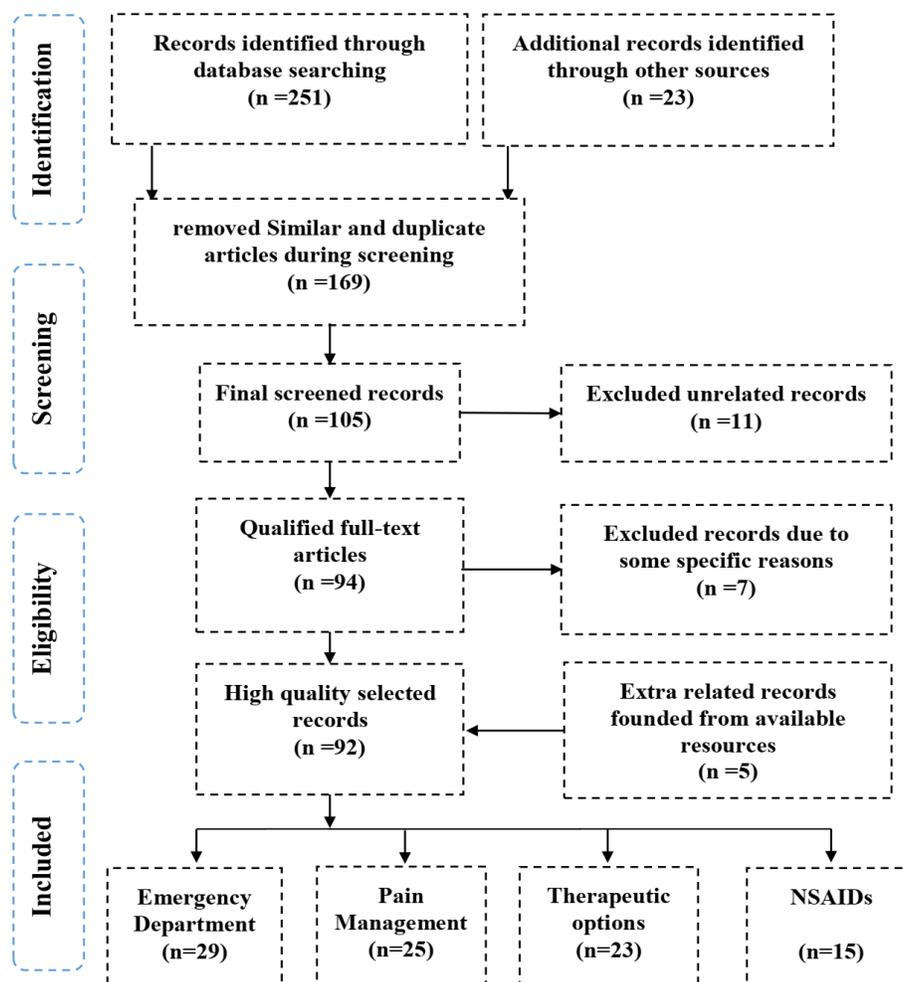


Figure 1. The schematic figure of screening, eliminating and selecting process of articles which reviewed within the present study based on the PRISMA method.

Table 1. The main causes of feeling pain among patients attended at the ED. Derived in accordance with [13].

Main causes of feeling pain												
Strain or joint sprain	Contusion, abrasion or/and wound	Neck or back pain	Abdominal pain	Dislocation or fracture	Headache	Noncardiac chest pain	Upper respiratory tract infections	Cellulitis and/or Abscess infections	Toothache	Acute renal colic	Urinary tract infection (UTI)	Other diagnosis
11	11	9	9	6	6	5	4	3	2	2	2	30
Occurrence rate (%)												

**Table 2. Potential cardiovascular and gastrointestinal side effects induced from the frequent application of NSAIDs. Derived in accordance with [32].**

			Possible side effects	
			Cardiovascular system	Upper gastrointestinal (GI) system
Nonsteroidal anti-inflammatory drug	Naproxen	HD	1.05	6.4
		LD	0.97	3.2
	Ibuprofen	HD	1.78	3.9
		LD	1.05	1.9
	Diclofenac	HD	1.98	4.2
		LD	1.22	2.5
	Celecoxib	HD	1.69	1.4
		LD	1.26	2.0
Nonsteroidal anti-inflammatory drug: NSAID Higher dosage: HD Lower dosage: LD				

**Table 3. Some available pharmacological options which frequently applied in ED situations for the management of acute pain. Derived in accordance with [82].**

	Opioid agents		NSAIDs		
Remedial option	Parenteral or/and oral	Intranasal therapy	Intranasal NSAIDs	Topical NSAIDs	Oral NSAIDs with quicker absorption
Type of pain	Multi-modality Pain	Multi-modality Pain	Multi-modality Pain	Local musculoskeletal pain	Multi-modality Pain
Advantages	For the treatment of pain at the range of moderate to severe	For the treatment of pain at the range of moderate to severe	Quicker relief of pain mainly in patients who cannot stand with oral NSAIDs	Effectively relief the pain even in a lower amount of dosage	Quicker and more effective pain relief even at lower doses
Limitation	Adverse effects like vomiting, dizziness, and constipation with the possibility of addiction	Needs higher concentration of local drug therapy	Their productivity is not much clear	Useful just for relieving local pain	Possibility of higher adverse effects