

Study on the main drugs and drug combinations of patient-controlled analgesia based on text mining

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Abstract

Background In recent years, with the continuous understanding of pain knowledge and the continuous improvement of quality of life requirements, patient-controlled analgesia (PCA) has been widely used in a variety of pain patients. In the treatment of PCA, more and more patients use multimodal analgesia (MMA). In this study, text mining technology was used to analyze relevant literatures, try to find out the main drugs of PCA, classify the drugs, and dig out the important drug combination rules. Methods PCA literatures were retrieved from Pubmed database in recent 10 years, and the bibliographic information of the literatures was taken as mining samples. First, the names of the drugs in the sample is identified by MetaMap package, then Bicomb software was used to extract high-frequency drugs for word frequency analysis and to construct a drug-phrase matrix. Finally, 'hclust' package and 'arules' package of R were used for cluster analysis and association analysis of drugs. Results 39 main PCA drugs were screened out, Morphine, Dexmedetomidine and Fentanyl were the top three drugs. Through cluster analysis, these drugs are divided into two clusters, one containing 26 common drugs and the other containing 13 core drugs. The association analysis of these drugs was carried out and 22 frequent itemsets and 6 association rules were obtained. The maximum frequent 1-itemsets were {Morphine} and the maximum frequent 2-itemsets were {Morphine, Ropivacaine}. Conclusions The research results have certain guidance and reference value for clinicians and researchers. In addition, it provides a way to study the relationship between drugs from the perspective of text mining.

Background

Pain is an unpleasant feeling and emotional sensation associated with existing or potential tissue damage and is listed as the fifth vital sign after temperature, pulse, respiration and blood pressure [1]. In recent years, with the continuous understanding of pain knowledge and the continuous improvement of quality of life requirements, patient-controlled analgesia (PCA) has been widely used in a variety of pain patients. Therapeutic approaches include intravenous PCA (PCIA), epidural PCA (PCEA), subcutaneous PCA (PCSA) and peripheral nerve PCA (PCNA) [2, 3]. The common drugs used in PCA are opioid analgesics, low-concentration local anesthetics and non-opioid analgesics, as well as some sedatives and antiemetic drugs. Opioids are the most commonly used analgesics in clinical practice [4], These drugs have side effects such as nausea, vomiting, tolerance and gastrointestinal dysfunction while treating pain. Respiratory inhibition is the main reason that limits the safety of opioids [5].

Multimodal analgesia (MMA) is the most effective analgesic strategy to reduce adverse reactions caused by a single drug or method, which combines various analgesic drugs and methods with different mechanisms to exert the best analgesic effect [6, 7]. In the treatment of PCA, more and more patients use MMA, and the types of drugs used and the ways of administration are more and more diversified. For example, Adding Ketamine to Morphine/Hydromorphone PCA provides a small improvement in postoperative analgesia while reducing opioid requirements. Adjunctive Ketamine also reduces postoperative nausea and vomiting without a detected increase in other adverse effects [8]. Adjunctive Parecoxib during Morphine combined with Ropivacaine epidural PCA (PCEA) following abdominal

hysterectomy is safe and efficacious in reducing pain [9]. The combination of Dexmedetomidine and Sufentanil for intravenous PCA (PCIA) after abdominal operation could reduce sufentanil consumption, decrease visual analogue scale (VAS) scores, lower the rate of nausea and vomiting, and improve patient satisfaction [10]. Faced with a large number of drugs and complex drug combination schemes, how to screen the main drugs in PCA and discover the combination rules of drugs and obtain valuable information from them becomes particularly important.

While a large number of experimental data are growing at an extraordinary rate, medical literature is also growing at an explosive rate. A large number of documents not only bring opportunities to obtain relevant information, but also contain many important links and rules. Therefore, they have also become data mining samples, resulting in text mining [11].

In this study, text mining technology was used to analyze PCA related literatures in the Pubmed database of the national library of medicine of the United States, so as to try to find out the main drugs of PCA, classify the drugs and dig out the important drug combination rules.

Methods

Data collection

From PubMed (<http://www.ncbi.nlm.nih.gov/PubMed>), we retrieved 735 relevant literatures using the terms “analgesia, patient-controlled [MeSH Major Topic]”, with no restriction on the language, the retrieval time span was 10 years and ended at 2019/06/08. The search results were saved in TXT format and used as the sample.

Drug identification

The drug names in the samples were identified by the MetaMap program [12] of National Medical Library (NLM). MetaMap is a natural language processing program developed by NLM. It can match free words in TXT format text to concepts in the Metathesaurus of the Unified Medical Language System (UMLS). It can compare words in abstracts with concepts in the super vocabulary and find matches through certain algorithms. And add a semantic type to each word.

Extracting identified drugs and constructing drug-phrase matrix

Word frequency analysis is an important means of text mining, which is a statistical analysis of the occurrence of important words in the text. Bicomb software [13] was used to extract the identified drugs, standardize the name of drugs and delete the names of drugs (such as Medicine, Opioid Agonist, etc.) which are too broad or unclear. The frequency of drug occurrence in the sample was counted and the drugs were arranged in descending order. Then, according to Pao's effective word frequency formula[14]

$T = [1 + (1 + 8I_1)^{1/2}] / 2$ (T is the dividing frequency of high-frequency words and low-frequency words, and I_1 is the number of words appearing once) to judge and screen drugs to find high-frequency drugs.

Then, the drug-phrase matrix is constructed by Bicomb software. If a drug appears in the phrase, it is marked as "1" and vice versa as "0". If two or more drugs co-occur in the same phrase, it is considered that there is a combination relationship between them.

Cluster analysis and association analysis based on R

There are many methods of text mining, among which clustering refers to classifying these data into different categories according to the similarity between the original data. Association analysis is to describe and analyze whether there are symbiotic phenomena in existing data, mainly reflecting the relevance between things, that is, the possibility of some events happening together.

In this study, we used the 'hclust' package [15] of R to cluster the generated discourse matrices, and gradually aggregate the close drugs into a number of conceptually independent classes. Through the study and interpretation of these classes, the current situation and rules of combination drug are analyzed and predicted.

Association analysis applied the 'arules' package [16] of R, and used the Apriori (a classic association rule algorithm) to conduct data association relation mining. The process consisted of two stages. Firstly, all frequent item sets were found from the drug-phrase matrix. Association rules were then generated from these frequent item sets. Through the interpretation of association rules, the tightest combinations of drugs were found.

Results

Results of high frequency drugs and drug-phrase matrix

Through the extraction of drug names from the bibliographic information, 83 PCA related drugs were obtained, including 19 drugs with frequency of 1. According to Pao's effective word frequency formula, 39 high-frequency drugs with a lowest frequency 7 were determined, and the cumulative word frequency contribution rate was 93.10%. Morphine, Dexmedetomidine and Fentanyl were the top three drugs (Table 1).

The drug-phrase matrix of 39 high-frequency drugs was constructed by Bicomb software, and 593 articles with co-occurrence relationship were obtained. Part of the matrix was shown in Table 2.

Results of system clustering

The clustering process was to integrate 39 drugs from small clusters to larger ones according to the distance, and the similarity within the cluster decreases gradually. The drugs in the smallest cluster can often be combined with drugs directly. In addition, we can make valuable discoveries by analyzing the nature or type of different clusters of drugs. The results of clustering are shown in Figure 1. According to the distance at the red line, the 39 drugs were generally divided into two big clusters.

The first cluster contains 26 drugs, with Propofol appearing 78 times at the highest frequency and Celecoxib appearing 7 times at the lowest frequency. Ketorolactic is the most widely used combination drug, which was related to eight drugs, and Litonavir, Methadone and Pregabalin are the least, which were related with only one drug.

The second cluster contains 13 drugs, with Morphine appearing 759 times at the highest frequency and Meperidine appearing 57 times at the lowest frequency. Morphine was the most abundant combination drug, which is related with 26 drugs, and Meperidine was related with 6 drugs at least.

Results of frequent itemsets and association rules

Apriori algorithm involves three important parameters, Support, Confidence and Lift. Support measures the universality of the application of association rules, and the higher the degree of Support, the more common the rule is adopted; Confidence reflects the accuracy of association rules, and the higher the degree of Confidence, the greater the opportunity of the latter item under the condition of the existence of the preceding item of the rule; Lift reflects the practicability of the association rules, only the Lift with a degree greater than 1 are useful. In order to obtain a certain number of association analysis results, we set the Support to 0.05 and the Confidence to 0.7.

After operation, we get 22 frequent itemsets. Among them, there are 12 frequent 1-item sets and 10 frequent 2-item sets. As shown in Figure 2, the larger the circle, the greater the Support. Each item points to the Support through a directed arrow, indicating that the relevant items constitute an itemset. In this case, the Support is 0.052–0.53. The maximum frequent 1-item set is {Morphine} with Support of 0.53; the maximum frequent 2-item set is {Morphine, Ropivacaine}, with support of 0.15.

In the analysis of association rules, we obtained six valuable association rules with Lift greater than 1. As shown in Figure 3, the larger the circle, the greater the Support, the darker the color of the circle, the greater the lift. Among them, {Ketamine} = > {Morphine} has the greatest Support, with the Support of 0.14; the greatest Lift is {Neostigmine} = > {Bupivacaine}, with the Lift of 5.12.

Discussion

Firstly, in word frequency analysis, 39 high-frequency drugs of PCA were obtained, Morphine, Dexmedetomidine and Fentanyl were the top three drugs, these drugs are the main drugs for PCA.

Through the drug-phrase matrix, we can find that 39 drugs all have co-occurrence relationship with other drugs, which indicates that drug combinations are common in PCA.

Secondly, in the systematic cluster analysis, two clusters of drugs were obtained. The first cluster was common drugs, which are rarely combined with other drugs and mainly used as adjuvant drugs. Most of them were Non-Steroidal Antiinflammatory Drugs, while a small amount of antiemetics and local anesthetics are also available. Generally speaking, they were difficult to use alone for PCA, so they should be combined with other powerful analgesics. The second cluster was core drugs, which are widely combined with other drugs and are the core analgesics of PCA. Most of them were opioid powerful analgesics, and there were also long-term local anesthetics, which are widely used, such as Morphine, Fentanyl, Ropivacaine, etc., they can be used as a single drug for PCA [17–19]. Among these drugs, Dexmedetomidine ranked second in frequency, is not an opioid and has both sedative and analgesic effects. It had a combination relationship with many drugs and played an important role in PCA combination drugs.

Finally, Apriori algorithm is applied to analyze the drug-phrase matrix, and 22 frequent itemsets and 6 association rules were obtained. Drugs in frequent itemsets were more closely related to the combination of other drugs. Among them, the maximum frequent 1-item set was {Morphine}, which indicates that Morphine has more combinations with other drugs. The maximum frequent 2-item set was {Morphine, Ropivacaine}, which indicates that 'Morphine+Ropivacaine' is more combined with other drugs in more than two drugs formulations. From the results of association rules, six closely related drug combinations were obtained. The most Supportive was {Ketamine} = > {Morphine}, which indicates that if Ketamine was used in PCA formulation, morphine would be more likely to be used in combination; the most Lift was {Neostigmine} = > {Bupivacaine}, which indicated that if Neostigming is used in the formulation, it was more reasonable to use Bupivacaine in combination.

There were some limitations in this study. In order to match the MetaMap program better, we only chose Pubmed database as the only source of literature data, we will add more medical professional database in the future research. In addition, due to the co-occurrence method used in the extraction of drugs, there was a lack of negative detection. Even if it was explicitly stated in the same phrase that there was no relationship between certain drugs, they were still be considered to have co-occurrence relationship, impacting the results of the study.

Conclusions

In the treatment of pain with PCA, people advocate MMA. The combination of different pharmacological analgesics can reduce the side effects of opioids and maintain adequate analgesic level. In this study, text mining technology was used to mine recent literatures on PCA, identify the main drugs, and analyze the core drugs in combination drugs and the association between them. The results of this study have certain guidance and reference value for clinicians and researchers. In addition, it provides a way to study the relationship between drugs from the perspective of text mining.

Abbreviations

PCA:Patient-controlled analgesia;MMA: Multimodal analgesia; PCIA: Intravenous PCA; PCEA: Epidural PCA; PCSA: Subcutaneous PCA; PCNA: Peripheral nerve PCA; VAS: Visual analogue scale; NLM: National Medical Library; UMLS: Unified Medical Language System.

Declarations

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Authors' contributions

XJ and YW conceived and designed the study. XJ and LH collected and cleaned the data. XJ and YW analyzed the data and drafted the manuscript. YW and LH revised the manuscript and interpreted the results. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 39 high-frequency drugs related to PCA

Rank	Drug name	Frequency	Rank	Drug name	Frequency
1	Morphine	759	21	Ondansetron	29
2	Dexmedetomidine	398	22	Acetaminophen	28
3	Fentanyl	360	23	Neostigmine	27
4	Remifentanil	333	24	Nefopam	27
5	Ropivacaine	162	25	Midazolam	25
6	Sufentanyl	129	26	Dexamethasone	21
7	Oxycodone	121	27	Lidocaine	19
8	Ketamine	107	28	Dezocine	19
9	Bupivacaine	105	29	Piritramide	19
10	Tramadol	99	30	Ramosetron	19
11	Propofol	78	31	Butorfanol	18
12	Hydromorphone	73	32	Tropisetron	15
13	Levobupivacaine	70	33	Pregabalin	14
14	Meperidine	57	34	Methadone	14
15	Paracetamol	47	35	Gabapentin	14
16	Parecoxib	46	36	Lornoxicam	11
17	Ketorolac	46	37	Dipyrone	9
18	Droperidol	36	38	Ritonavir	8
19	Clonidine	36	39	Celecoxib	7
20	Alfentanyl	33			

Table 2 Part of the drug-phrase matrix

Drug name	7576	7577	7578	7580	7581	7600	7601	7602
Morphine	0	1	1	1	1	0	0	0
Dexmedetomidine	0	0	0	0	0	0	0	0
Fentanyl	0	0	0	0	0	1	0	0
Remifentanil	0	0	0	0	0	0	0	0
Ropivacaine	1	1	0	1	0	0	1	0
Sufentanyl	0	0	0	0	0	0	0	1
Oxycodone	0	0	0	0	0	0	0	0
Ketamine	0	1	0	0	0	1	0	0
Bupivacaine	0	0	0	0	0	0	0	0

Figures

Cluster Dendrogram

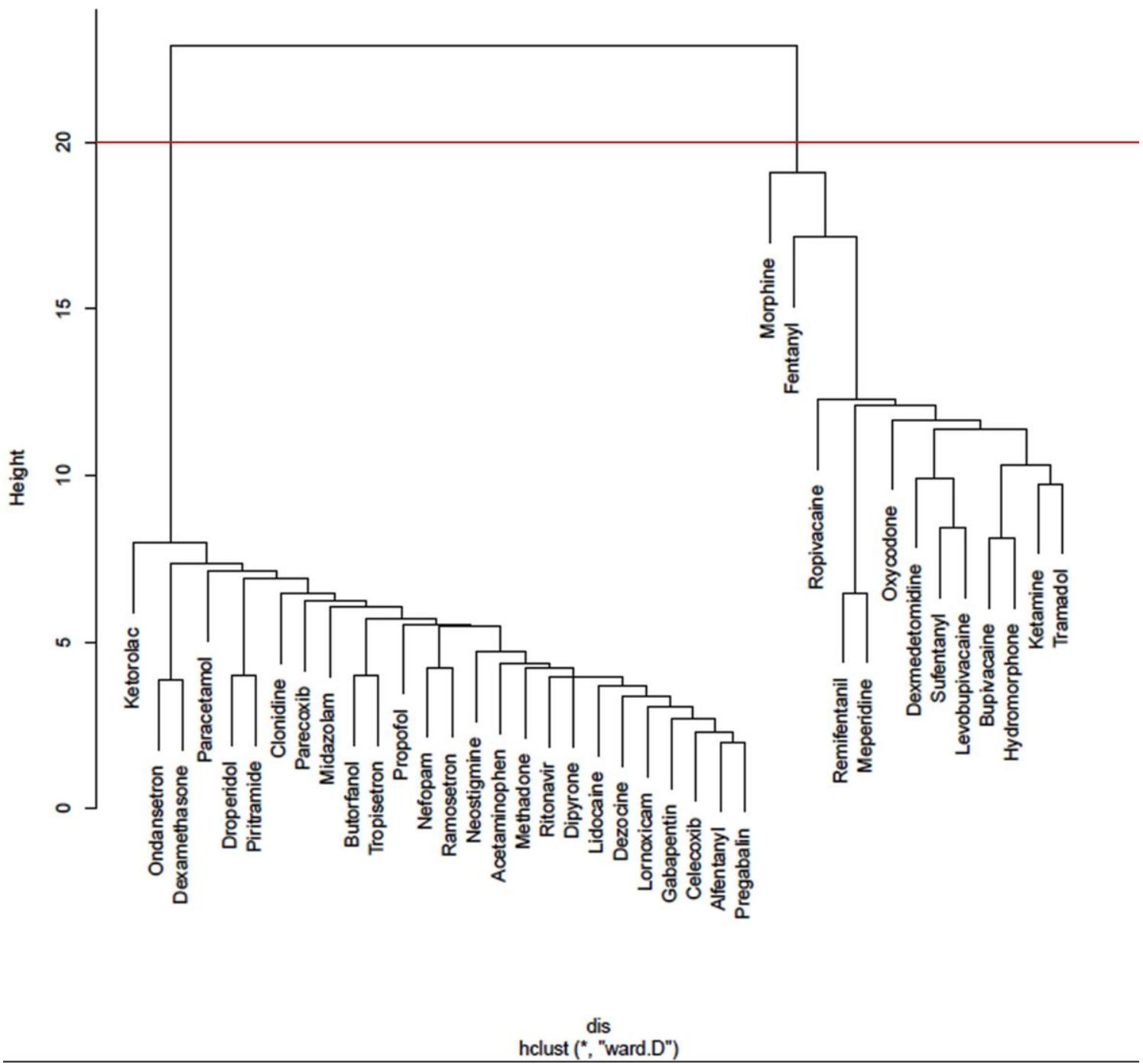


Figure 1

Cluster dendrogram of 39 high-frequency drugs related to PC

Frequent itemsets

size: support (0.052 – 0.53)

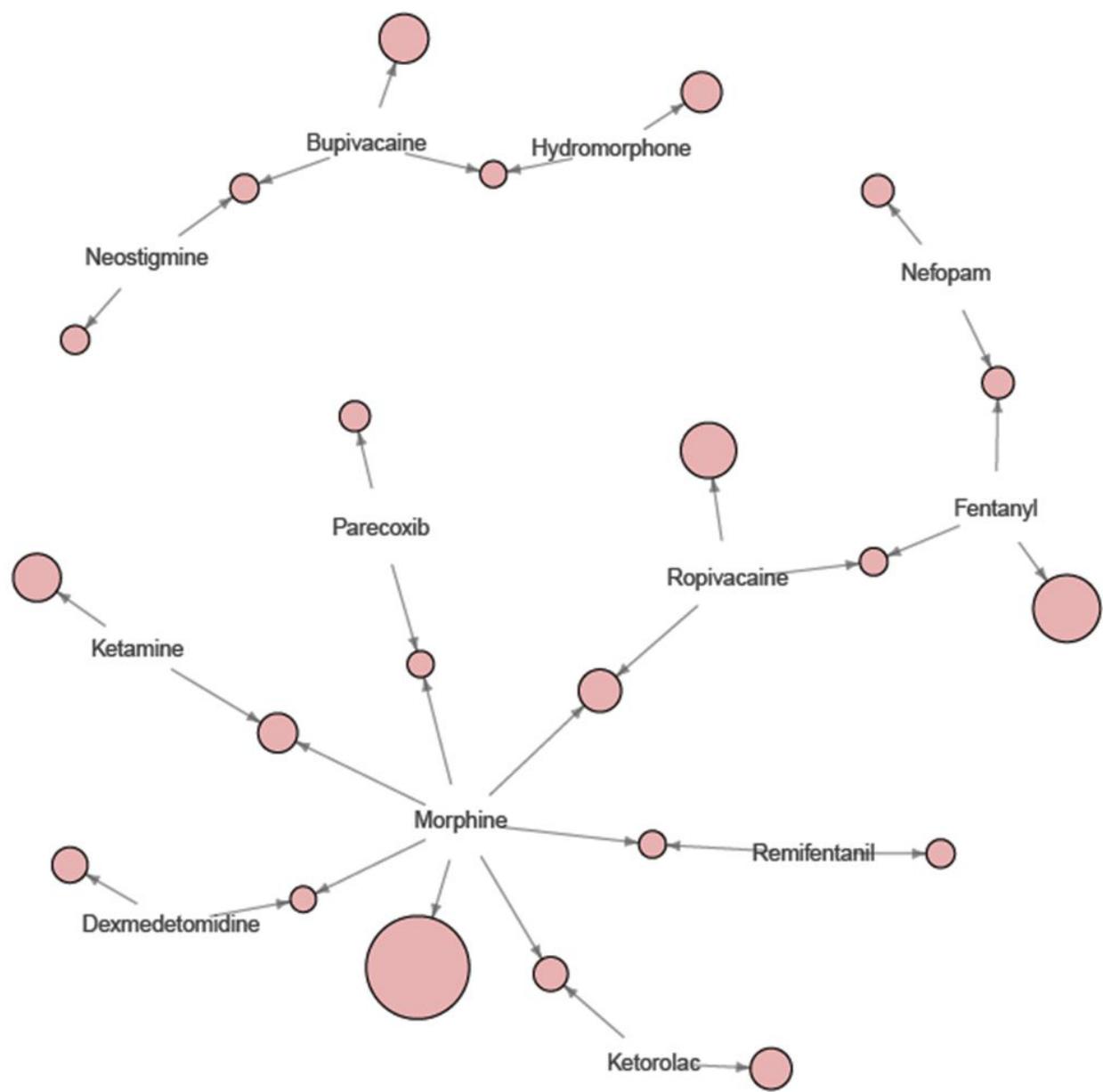


Figure 2

The visualization map of 22 frequent itemsets

Grouped Matrix for 6 Rules

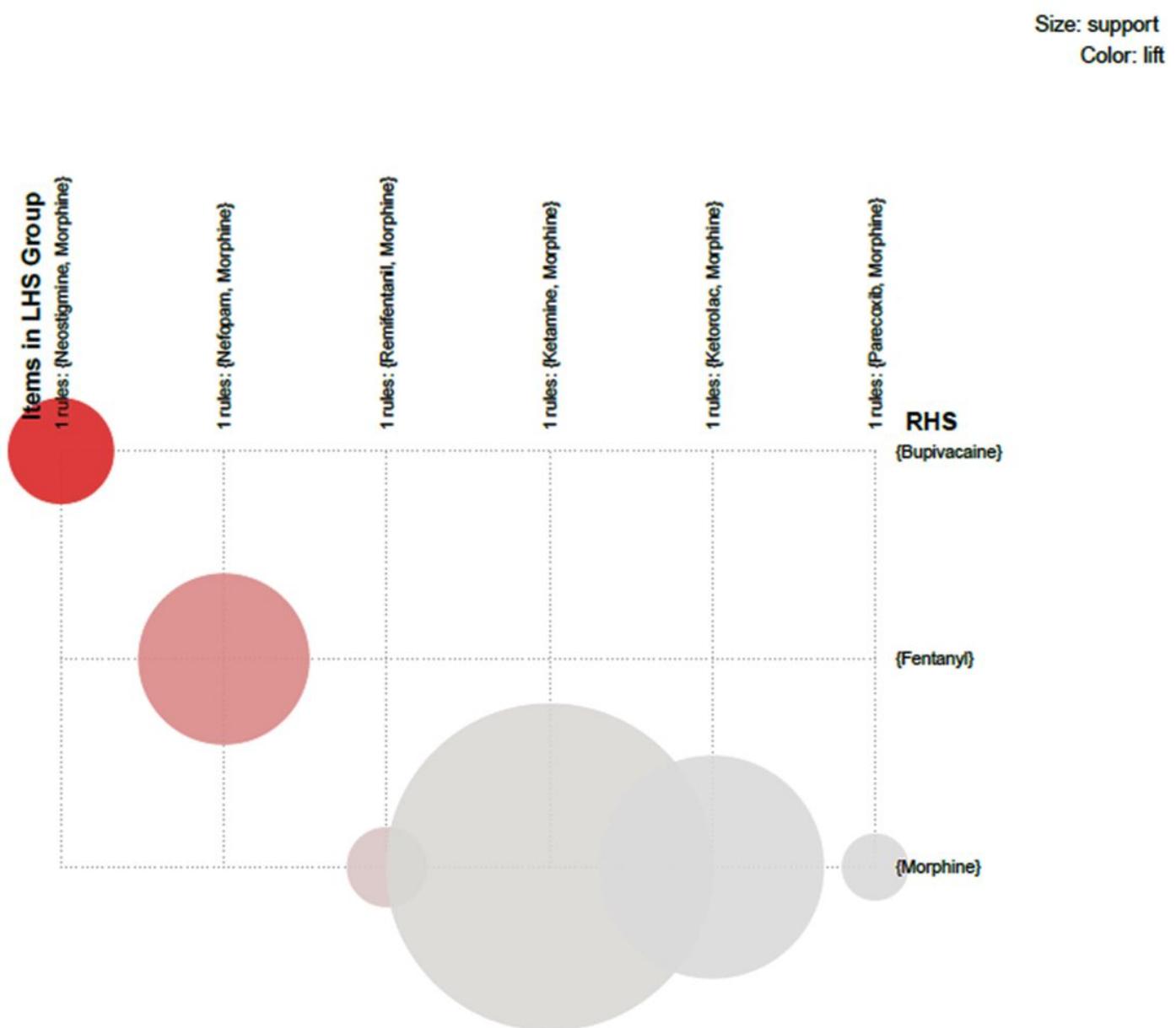


Figure 3

The visualization map of 6 association rules