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LOGISTIC REGRESSION MODELS FOR JAPANESE BLUNT TRAUMA VICTIMS

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This study investigated logistic regression models that would offer better survival prediction of Japanese blunt trauma (BT) victims, and demonstrate the probability of survival (Ps) without RR data on admission. Using calculable data for Ps (12,975) from BT patients (17,564), registered in the Japan Trauma Data Bank (JTDB) (2004～2007), we allocated a random half (6,487) of the data to a training data set, and the remaining half (6,488) to a validation data set. For logistic regression analysis, age, injury severity score (ISS), Glasgow coma scale score (GCS), systolic blood pressure (BP), respiratory rate (RR), and their coded values (cBP, cGCS, cRR) were used as independent variables. For validation, areas under curves (AUCs) of receiver-operating characteristic curves were compared. Ps data that were not computable (4,574) were used for external application of the models. The model with ISS, age, cBP, cGCS, and cRR shows the best AUC of 0.9674 in the training data, and 0.9670 in the validation data. A similar model without cRR shows AUCs of 0.9670 and 0.9654. Application of the model to patients with missing RR data demonstrated an AUC of 0.9023. The model using ISS, age and cBP, cGCS, cRR seems to offer the best survival prediction. The model without cRR can be used, if RR data are not available.

Key words：JTDB, TRISS, non-penetrating trauma, respiratory rate

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Influence of Loxoprofen Use on Recovery from Naturally Acquired Upper Respiratory Tract Infections: A Randomized Controlled Trial

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Abstract

Objective: To investigate whether loxoprofen, one of the nonsteroidal anti-inflammatory drugs, prolongs the recovery process of naturally acquired upper respiratory tract infections (URTIs) in the clinical setting.

Methods: A double-blind, randomized, placebo-controlled trial was conducted in 23 outpatient facilities in Japan. Patients aged 18 through 65 years suffering from URTIs were randomly assigned to receive loxoprofen or its placebo. The primary outcome was duration of illness in days.

Results: A total of 174 patients were available for the analyses. Duration of illness was 8.94 ± 3.20 days in the loxoprofen group compared to 8.39 ± 3.39 days in the placebo group (P=.19). The number of days with limited daily activities was fewer in the loxoprofen group than in the placebo group (2.12 ± 2.05 days vs. 2.68 ± 2.54 days, P=.17). Although severe symptoms were less frequent on days 1, 2, and 3 in the loxoprofen group (27%, 33%, and 29%, respectively) than in the placebo group (32%, 39%, and 37%, respectively), symptoms were more frequent on days 6 through 12 in the loxoprofen group (difference, 5-13%). Adverse events were more common in the loxoprofen group (9.5% vs. 1.1%, P=.051).

Conclusion: Loxoprofen did not significantly modify the recovery process of URTIs except for a slight tendency to delay.

Key words: common cold, non-steroidal anti-inflammatory agents, loxoprofen

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Introduction

Upper respiratory tract infections (URTIs) are the most frequent acute illness throughout the industrialized world. (1) Although it is associated with an enormous economic burden both in lost productivity and in expenditures for treatment (2), the most appropriate means of management has not yet been thoroughly established. Usage of nonsteroidal anti-inflammatory drugs (NSAIDs) remains controversial. Although NSAIDs would improve acute URTI symptoms such as fever and various types of pain, they could adversely affect the healing stage because they suppress the inflammatory reaction which serves to repair infection-induced acute tissue injury (3).

There have been two types of study populations used to evaluate the effectiveness of NSAID treatments for URTIs. One is experimentally infected subjects and the other is naturally infected ones. Studies of the former type yielded conflicting results. Stanley et al (4) and Graham et al (3) reported that the period of viral shedding increased and immune responses were suppressed by use of NSAIDs.

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Mogabgab and Pollock (5), Hsia et al (6) and Sperber et al, (7, 8) meanwhile, denied influences of NSAIDs on viral shedding. Studies of naturally occurring URTIs (9-12), however, have uniformly focused on the severity of acute symptoms such as nasal discharge, fever, and headache, and little attention has been paid to the duration of illness. Only one study using acetaminophen which has poor anti-inflammatory activity (13) evaluated the duration of symptoms among young children with fever of presumed viral origin (14).

Loxoprofen is a 2-arylpropionic acid anti-inflammatory agent with analgesic and antipyretic properties. It is a prodrug which hardly causes any gastrointestinal problems, and is widely used in Japan. This randomized controlled trial (RCT) was aimed to investigate whether or not loxoprofen prolongs the recovery process of naturally acquired URTIs.

Methods

A double-blind, randomized, placebo-controlled trial was conducted in 23 outpatient facilities including 11 university student health centers, outpatient departments of five university hospitals and two community hospitals, and five private practices during two consecutive winter seasons: from December 1 through March 31, in both 2002-2003 and 2003-2004.

Study participants

Patients aged 18 through 65 years who exhibited symptoms or signs in both nose (rhinorrhea, nasal congestion, sneezing, or snuffling) and pharynx (sore throat or pharyngeal redness), and visited physicians within 48 hours after symptom onset were enrolled in the study.

Patients who were clinically thought to suffer from influenza, pneumonia of any cause, β-streptococcus tonsillitis, and other bacterial infections were excluded. Patients with serious or confusing underlying diseases including bronchial asthma, peptic ulcer, diabetes mellitus, and allergic rhinitis were also excluded from the study as well as immunocompromised or pregnant persons. Patients who were currently using antibiotics, systemic corticosteroids, immunosuppressants, or anticoagulants, and those who had taken NSAIDs or Chinese herbal medicines as cold remedies within 12 hours were ineligible for the study. Written informed consent was obtained from all participants.

Intervention

Each participant was randomly assigned to one of the two treatment arms, intervention and control, by self-drawing a sealed opaque envelope in the physician's sight. Randomization was based on simple computer-generated random digits and the correspondence between the digits and the group assignment was held in the central, secured location by a third party independent of the investigators until data collection was completed. Thus, allocation was concealed and masked from both patients and physicians.

Patients in the intervention group were to take loxoprofen sodium (60 mg/tablet) and those in the control group were to take a placebo which was quite similar to active loxoprofen in shape and taste. In addition to loxoprofen or its placebo, an antihistamine, mequitazine (3 mg/tablet), were also prescribed for both group members. As a rule, participants were to take one tablet of each drug twice a day for at most seven days. They were allowed to increase the daily dose of drugs up to three tablets per day for each drug or decrease and even discontinue them depending on their symptoms. Participants were forbidden to take any other drugs during the study period. However, when they revisited the doctor due to persistence or progression of symptoms, they were allowed to be prescribed other drugs depending on their complaints.

Follow-up

All subjects were requested to fill in the prescribed form (URTI diary) every day from the onset of illness. This form included various URTI complaints such as nasal symptoms (rhinorrhea and sneezing), pharyngeal symptoms (soreness and scratchiness), bronchial symptoms (cough and phlegm) and general symptoms (feverishness, arthralgia, and malaise). Each symptom was classified into four grades, i.e., "none," "mild," "moderate," and "severe," according to the Jackson method (15). "Mild" was defined as when a subject was unaware of the symptom when he/she was busy with something; "moderate" as when one always felt discomfort; and "severe" as when one experienced difficulties in daily life. When a patient felt feverish, he/she was to measure body temperature and record the highest value of the day. Restriction of daily activities was also graded as "none," "partly restricted," "considerably restricted," and "absent from duty." General physical condition was rated on a one-to-ten scale: from 1 (extremely bad) through 10 (extremely good). Adverse events were asked in an open-ended manner. When remedies other than the study drugs were given to the study patients, physicians were to describe the prescription in the URTI diary.

Participants were required to revisit physicians one week later or after recovery to return the URTI diary and unused drugs. If a patient did not make the second office-visit, his/her physician telephoned to remind him/her.

Statistical analysis

Baseline (at the initial office visit and randomization) characteristics and outcome measures were compared between two groups using Student's *t*-test for continuous variables, and Pearson's chi-square test for categorical variables. When the severity of symptoms was evaluated, each symptom grade was replaced by numerical scores, i.e., "none" as 0, "mild" as 1, "moderate" as 2, and "severe" as 3, and Wilcoxon rank sum test was applied. Proportions of rare events were assessed by Fisher's exact test. Daily changes in illness were compared by fitting repeated binary responses to a generalized linear model (16), where treatment group, day

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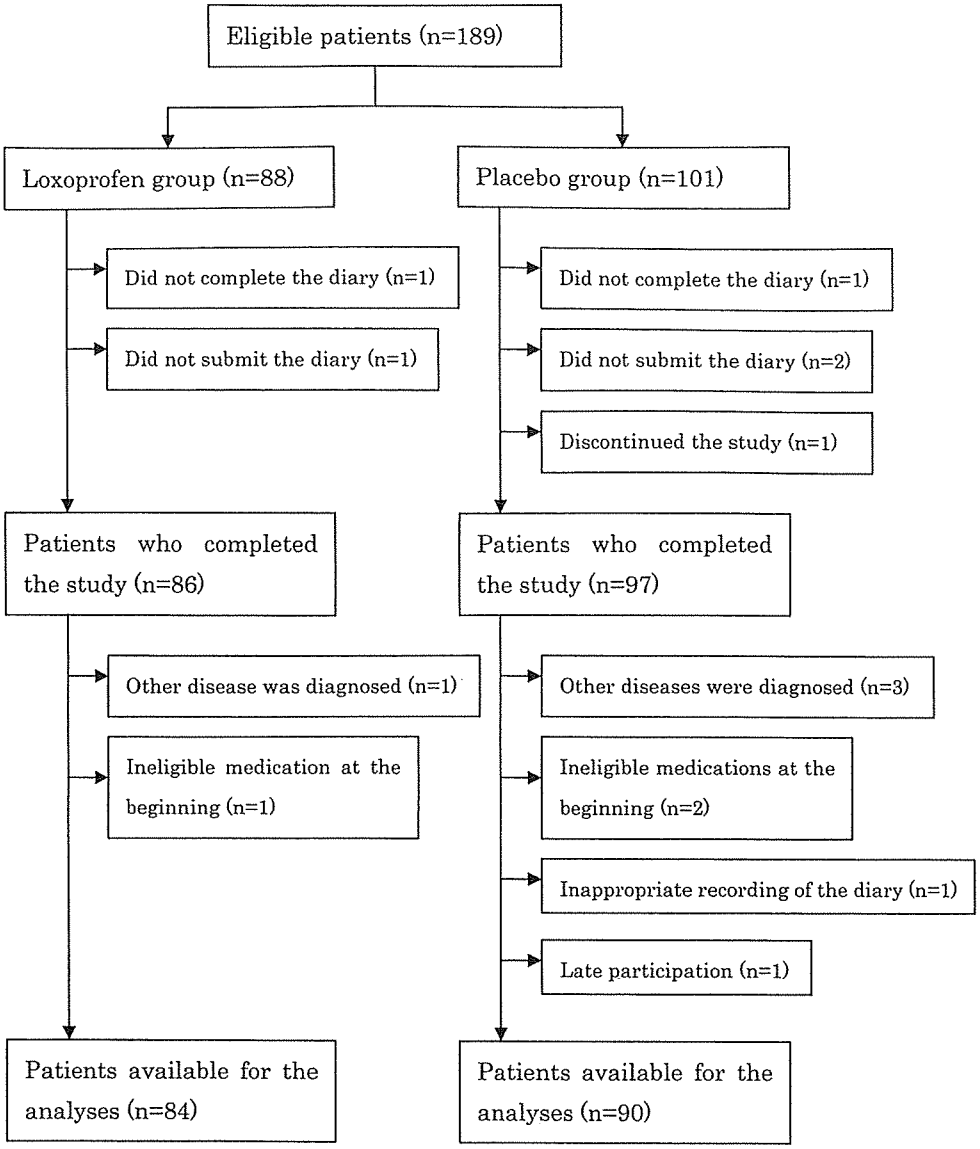

Figure 1. Flowchart of the study.

of illness, and interaction between group and day of illness were included.

The primary outcome measure of this study was the interval in days from the onset of any URTI symptom to the disappearance of all URTI symptoms. The secondary outcomes were severity of URTI symptoms, including general physical condition and performance in daily activities. A power calculation indicated that a sample of 85 per group was necessary to detect a difference in duration of illness between 7 and 8.5 days (7), where power was set at 90%; 2-sided P-value, .05; and standard deviation, 3.0.

Statistical analyses were performed using Stata8.0 (Stata Corporation, College Station, TX, 2003) for univariate analysis and linear regression analysis, and SAS9.1 (SAS Institute, Cary, NC, 2004) for multivariate longitudinal analysis. P values were calculated controlling for possible confounding factors when needed, and the threshold level of .05 was considered statistically significant. All analyses were on an intention-to-treat basis. This study protocol was approved by the Ethics Committee of Kyoto University Faculty of Medicine (No. 404, October 29, 2002).

Results

Figure 1 is the flow chart of this study. A total of 189 patients were randomly assigned to loxoprofen (n=88) and placebo (n=101) groups. Of the 189 participants, six (two in loxoprofen group and four in placebo group) withdrew from the study, because two patients (one in loxoprofen and another in placebo) did not complete the diary, three patients (one in loxoprofen and the others in placebo) did not return the diary, and one patient (placebo) decided not to continue the study after the allocation. We excluded nine more participants (two in loxoprofen and seven in placebo) from analyses, because influenza or acute sinusitis were diagnosed after allocation (one in loxoprofen and three in pla-

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Table 1. **Baseline Characteristics of Participants in Loxoprofen and Placebo Groups**

	Loxoprofen	Placebo
No. of patients	84	90
Age (years)	29.3 ± 12.5	27.6 ± 11.4
Sex (proportion of men, %)	65.5	65.6
Proportion of smokers (%)	32.8	26.1
Severity of symptoms (scored 0 to 3) *		
Headache	0.71 ± 0.83	0.78 ± 0.89
Rhinorrhea	1.50 ± 0.88	1.67 ± 0.94
Nasal congestion	1.19 ± 0.94	1.35 ± 0.98
Sneezing	0.70 ± 0.72	0.73 ± 0.79
Sore throat	1.51 ± 0.84	1.52 ± 0.95
Scratchiness	1.42 ± 0.91	1.38 ± 0.91
Hoarseness	0.86 ± 0.92	0.82 ± 0.90
Cough	1.15 ± 0.95	1.02 ± 1.00
Phlegm	0.86 ± 0.93	0.73 ± 0.86
Arthralgia/myalgia	0.61 ± 0.86	0.57 ± 0.88
Chilliness	0.65 ± 0.86	0.87 ± 0.89
Feverishness	0.93 ± 0.80	1.12 ± 0.90
General malaise	1.07 ± 0.90	1.20 ± 0.99
Restriction of daily activities (scored 0 to 3) †	0.67 ± 0.84	0.85 ± 0.92
General physical condition (1-to-10 scale)	4.70 ± 1.84	4.99 ± 1.85
Body temperature (℃)	36.9 ± 0.59	36.8 ± 0.70

* "None" was replaced by 0, "mild" by 1, "moderate" by 2, and "severe" by 3.

† "None" was replaced by 0, "partly restricted" by 1, "considerably restricted" by 2, and "absent from one's duty" by 3.

Table 2. **Symptoms, Use of Drugs, and Adverse Events in Loxoprofen and Placebo Groups**

	Loxoprofen	Placebo	P-values	
			Univariate analysis	Multivariate analysis*
No. of patients	84	90		
Duration of illness (days)	8.94 ± 3.20	8.39 ± 3.39	0.18	0.19
Duration of symptoms (days)				
Headache	2.65 ± 2.92	2.77 ± 3.08	0.93	0.63
Rhinorrhea	6.73 ± 3.78	6.78 ± 3.66	0.93	0.55
Nasal congestion	5.71 ± 3.70	5.89 ± 4.04	0.83	0.86
Sneezing	3.37 ± 3.12	2.56 ± 2.71	0.072	0.096
Sore throat	5.46 ± 3.27	5.00 ± 3.12	0.28	0.28
Scratchiness	5.39 ± 3.42	5.11 ± 3.39	0.64	0.77
Hoarseness	3.89 ± 3.37	3.54 ± 3.31	0.47	0.35
Cough	5.61 ± 4.10	4.99 ± 4.03	0.28	0.31
Phlegm	4.80 ± 3.76	4.02 ± 3.73	0.14	0.16
Arthralgia/myalgia	1.76 ± 2.41	1.97 ± 2.67	0.88	0.34
Chilliness	2.12 ± 2.59	2.40 ± 2.50	0.34	0.37
Feverishness	2.92 ± 2.70	2.96 ± 2.30	0.59	0.70
General malaise	3.58 ± 2.93	3.56 ± 2.89	0.94	0.92
Total symptom score during diseased period	76.4 ± 45.6	75.1 ± 48.0	0.85	0.78
Duration of restriction of daily activities (days)	2.12 ± 2.05	2.68 ± 2.54	0.17	0.17
Average score of general physical condition (1-to-10 scale)	6.35 ± 1.38	6.55 ± 1.32	0.26	0.39
Maximum body temperature (℃)	37.2 ± 0.79	37.2 ± 0.75	0.37	0.68
Consumption of study drugs: Loxoprofen / Placebo (tablets)	11.0 ± 5.01	9.85 ± 4.87	0.12	0.14
Consumption of mequitazine (tablets)	10.1 ± 5.85	9.99 ± 5.01	0.79	0.71
Proportion of patients to whom other drugs were prescribed (%)	10.7	18.9	0.14	0.11
Proportion of patients with adverse events (%)	9.5	1.1	0.015	0.051

* Adjusted for age, sex, smoking, type of the facilities, region, and the year when the patient was included.

cebo), antibiotics or Chinese herbs were used just before the initial visit (one in loxoprofen and two in placebo), recording of the diary was inappropriate (one patient in placebo), and the initial visit was 6 days after the onset (one patient in placebo). Therefore, the remaining 174 patients (84 in loxoprofen and 90 in placebo) were available for the analyses. Table 1 shows the baseline characteristics of the study patients. There was no significant difference in age, sex, and severity in symptoms at randomization between the groups.

Table 2 summarizes the symptoms. Duration of illness, the number of days from the onset to the complete disappearance of URTI symptoms, was 8.94 ± 3.20 days in the loxoprofen group compared with 8.39 ± 3.39 days in the placebo group (P=.19). While sneezing and productive

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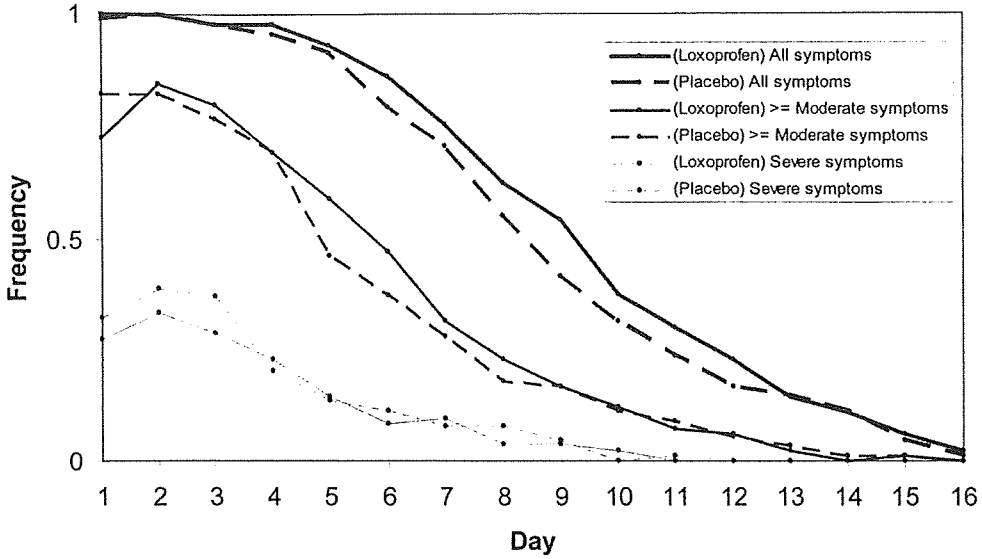

Figure 2. Changes in frequency of overall symptoms according to severity and day of illness.

cough tended to continue longer, days with limited daily activities were fewer in the loxoprofen group than in the placebo group (2.12 ± 2.05 days vs. 2.68 ± 2.54 days, P=.17). Total symptom scores during the diseased period were then almost identical between the two treatment groups (76.4 ± 45.6 in the loxoprofen group vs. 75.1 ± 48.0 in the placebo group, P=.78).

Figure 2 demonstrates the changes in frequency of overall symptoms according to severity and day of illness. Severe symptoms of any kind were less frequent on days 1, 2, and 3 in the loxoprofen group (27%, 33%, and 29%, respectively) than in the placebo group (32%, 39%, and 37%, respectively) even though statistically insignificant (P=.49, .45, and .26, respectively). Symptoms regardless of grade were, however, more frequent on days 6 through 12 in the loxoprofen group than in the placebo group (difference, 5-13%; P=.10-.46).

Change in frequency of each symptom with the day of illness was examined by the generalized linear model. Moderate or severe sneezing was more frequent in the recovery phase of illness, after day 3, in the loxoprofen group than in the placebo group (P=.011), whereas moderate or severe headache, severe arthralgia, and severe chills were less frequent (P=.001, .006, and .018, respectively) in the acute phase of illness, days 1 through day 3.

The number of loxoprofen tablets taken during illness was greater than that of placebo tablets (11.0 ± 5.0 tablets vs. 9.9 ± 4.9 tablets, P=.14; Table 2), although the consumption of mequitazine was similar in both groups (10.1 ± 5.9 tablets vs. 10.0 ± 5.0 tablets, P=.71). However, other drugs were less likely to be prescribed in the loxoprofen group than in the placebo group (10.7% vs. 18.9%, P=.11). Drugs additionally prescribed included acetaminophen (five in loxoprofen and six in placebo), other antihistamines (six in loxoprofen and 10 in placebo), and antitussives (two in loxoprofen and six in placebo). Some NSAIDs were prescribed for two cases of the placebo group. Most of those drugs were taken after day 8; otherwise, they were used within 2 days of the first visit.

Eight patients in the loxoprofen group (9.5%) complained of several kinds of adverse events including drowsiness (in three) and thirst (in two) during the follow-up period, which was higher than the one patient in the placebo group (1.1%) with drowsiness (P=.051, Table 2).

Discussion

This randomized placebo-controlled trial suggested that use of loxoprofen may slow down the recovery from URTIs (by approximately 13 hours) instead of providing some alleviation for severe symptoms and improved performance in daily activities, even though most of the effects were statistically insignificant. It also demonstrated that loxoprofen could increase adverse events.

Several studies on experimentally infected subjects suggested that the period of viral shedding increased by use of NSAIDs (3, 4). These findings are consistent with the theoretical inference from the fact that NSAIDs suppress biological responses essential to eradicate pathogens (13). Studies of naturally occurring URTIs (9-12), however, did not examine the duration of URTI symptoms. An RCT showed that acetaminophen which has little anti-inflammatory activity (13) did not change the duration of fever and other symptoms (14). Thus, this is the first RCT that examined how an NSAID would affect the recovery process of naturally acquired URTIs in clinical settings. Although loxoprofen is not available in most western countries, these findings are still worthwhile due to the frequent use of similar NSAIDs for uncomplicated URTI patients throughout the world.

The loxoprofen-induced clinical effects were smaller than expected. We performed the sample size calculation based on a study of an experimental infection model. In naturally acquired URTIs, there might be a wide variation in their na-

ture and clinical profiles. Another presumable reason is the relatively low dose of loxoprofen used in this study. Although three tablets of loxoprofen had been used daily in the phase-III clinical trial for the Government approval (17), we set the standard dose at two tablets daily in this study to reduce adverse events. This restriction could attenuate the difference of the effects. A study with larger sample size and heavier dosing might yield definite results. However, the present findings should help clinicians and patients make clinical decisions. Then, further studies are not necessarily required from the ethical point of view.

Several patients in the loxoprofen group complained of adverse events during the follow-up period as compared with only one in the placebo group. Most complaints, however, were deemed to be mequitazine induced. There may be some synergistic effects between mequitazine with loxoprofen, although to our knowledge, no report has been made on the pharmacokinetic or pharmacodynamic interaction between co-administered loxoprofen and mequitazine. In any case, clinicians should pay attention to the negative side of the drugs.

Other drugs such as antihistamines and antitussives were prescribed more frequently among the placebo patients than the loxoprofen patients. This fact may be attributed to a lower frequency of symptoms on day 6 through day 12 in the placebo group. However, most of the drugs additionally prescribed were taken after day 8 or just after the initial visit. Therefore, the influence of additional medications would be minimal on day 6 through day 8.

The present study has some admitted limitations. First, all of the outcomes measured were solely based on the patients' self-report, and no objective markers were used except for body temperature. However, their uncertainty was equal in both treatment groups because of the blindness, and comparability was ensured. Second, other diseases such as influenza and some bacterial infections were not completely ruled out, because diagnosis of URTIs was made only by subjective symptoms and physical findings. Since complete diagnosis is costly and even influenza and β-hemolytic streptococcus infections are self-limited in healthy people, symptom/sign-based diagnosis would be acceptable in community healthcare settings. Third, generalizability of our results was somewhat limited by the strict inclusion/exclusion criteria. Drug effects on patients who develop URTIs two days before or earlier and those with underlying diseases are unknown. In addition, our results are not applicable to children and elderly patients.

In conclusion, loxoprofen, one of the NSAIDs, did not significantly modify the recovery process from URTIs among naturally infected patients except for a slight tendency to delay complete recovery.

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I. 総　　論

臨床研究支援センターの機能と役割

Function and role of data management center for clinical research

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はじめに

診療を支えるエビデンスを作るため，臨床医自らが臨床研究を企画し実施することがある．しかし，多施設共同の医師主導臨床研究には，大きなバリアが存在する．このような研究を支援するのが，臨床研究支援センターである．本稿では，医師主導臨床研究の開始を考慮している臨床医にとって，研究の前後で必要となる作業を概観する．そして，臨床研究支援センターの機能と役割について解説する．また臨床研究のデータマネージメントを実施してきた日本臨床研究支援センターJCRAC/臨床研究データセンターの活動について紹介する．

なお，臨床研究支援センターという名称は，特に法的な実体をもつものではない．大学や病院内などで，様々な機能をもつ組織が作られている．本稿では臨床研究支援センターとして，広義のデータセンター機能も有し，臨床研究の基盤となる組織を考慮した．治験の場合であれば，治験の実施を助けるものとして，開発業務受託機関(Contract Research Organization: CRO)がある．このCROに該当する機能をもつ組織を考慮した．

また，本稿で臨床研究支援センターの対象としたものは，臨床試験のみではなく，臨床疫学的な観察研究を含む臨床研究全般である．このため，臨床試験より臨床研究という表現を多用した．

1. 治験と医師主導臨床研究との対比

治験はGCPなどに基づき，整備された体制のもとで実施されるが，医師主導の臨床研究では様子を異にする．まずこの違いを考えてみたい(図1)．

a. 治験の実施体制

治験はあくまで医薬品の新規承認申請を目指して実施される．通常，製薬企業が治験依頼者，スポンサーとなる．製薬企業自らがGCPで規定しているスポンサーの役割を果たす．そして治験実施の支援をCROに委託し，臨床薬理試験から検証的試験といった臨床試験や市販後調査などを実施する．そして患者登録，モニタリング，データマネージメント，統計解析，メディカル・ライティング，監査などの機能を果たす[1]．病院内では治験管理室が設置されCRCが配置されて，多忙な臨床医を支援する．治験依頼者は十分な実施基盤をもつ施設と契約し，かつ，実施経験，サポート体制を有しているといえる．

b. 医師主導臨床研究の実施体制

医師主導の臨床研究は，臨床医が自ら研究責任者となって研究費を獲得しスポンサーとなり，実施される．既に市販された医薬品などについ

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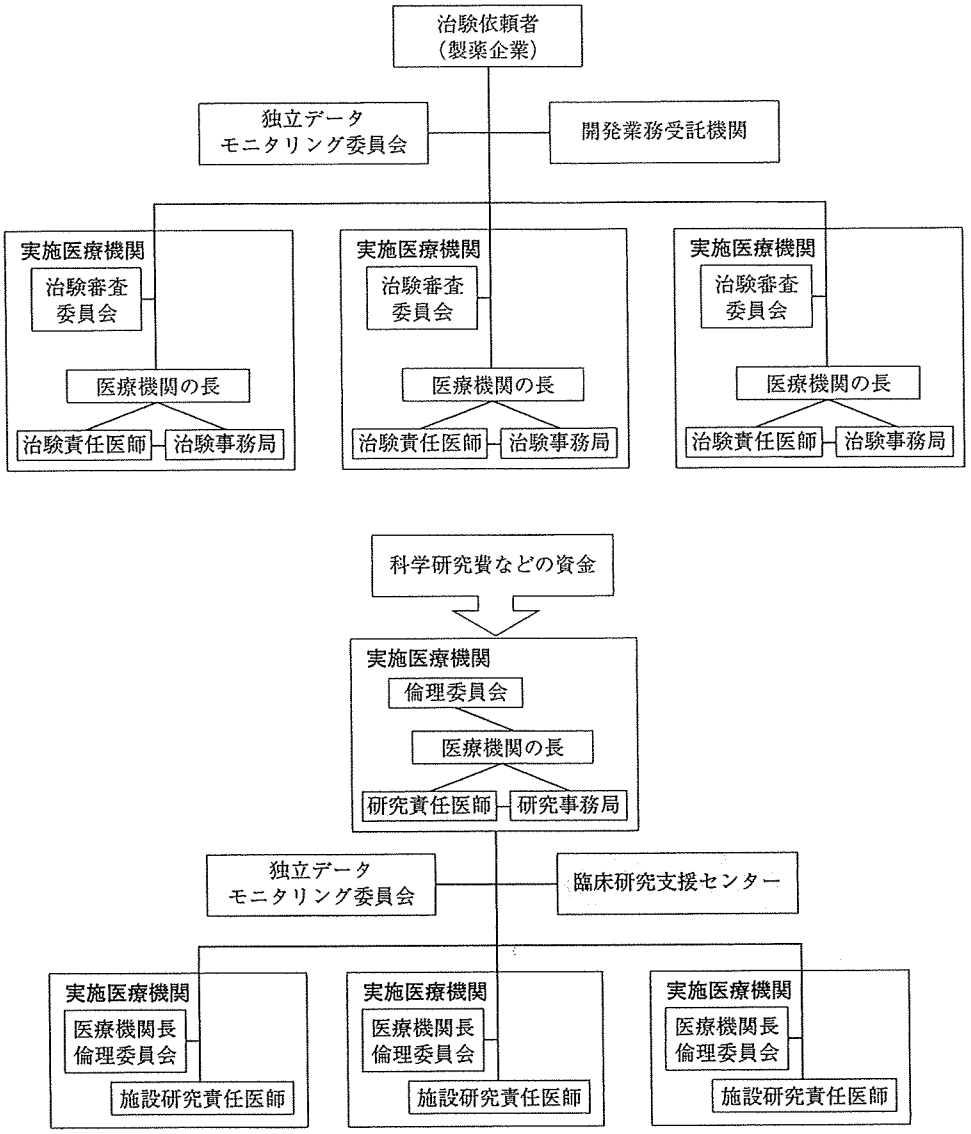

図1 治験と医師主導臨床研究の実施体制の対比
(上：治験，下：医師主導臨床研究)

ての研究でも，診療上の更なる疑問に答えるために実施される．治療のみではなく診断方法の研究や，医療の質の評価に属する研究も実施される．用いられる研究デザインとして，介入研究のみではなく観察研究も含まれる．医療の質の向上には，治験以外の臨床研究も必須である．

医師主導の臨床研究では，研究体制を臨床医が自ら構築しなければならない．また，施設と契約を結ぶことがなく，厚生労働科学研究費補助金のように各施設の研究者個人宛に研究費が支払われるため，スポンサーである医師が，GCPで規定している製薬企業の役割に該当する責任を自ら負う．そして実務的な作業や研究組織の運営を行う．しかし，臨床研究に関する倫理指針に多施設共同研究を実施する場合のセントラル機能の役割について記述はなく，ま

た通常臨床医には，臨床研究に関する実務の知識・経験は蓄積されていない．どのようにしてデータの収集・保管・管理を行い信頼性があり解析に足るデータベースを作成するのか，また研究の進捗をどのようにモニタリングするのか，不慣れである．このような作業を支援するのが臨床研究支援センターであり，治験でのCROに該当する．

医師主導の臨床研究でも，CROに委託可能である．ただし，CROは治験による収益が大きく，手続きとしての治験の進め方についての経験に偏っている可能性がある．臨床医がエビデンスとして欲する研究は多様である．また，研究計画で規定した治療の中止後にもエンドポイントに関する観察は継続するなど，施設内のCRCも不慣れなことがある．臨床研究の実施に際して，多様な研究の経験が蓄積された臨床研究支援センターの果たす役割は大きい．

2. 臨床研究支援センターの機能

臨床研究支援センターとして，この項ではデータセンター機能を含む組織を想定した．そしてその一般的な機能の例を**表1**に記載した．臨床研究が学会や論文として発表される場面を表舞台とすれば，臨床研究支援センターは舞台裏，楽屋に相当する．

臨床研究支援センターを構成する職種は，生物統計家，臨床疫学者や疫学者，研究デザインに通じる臨床医，薬剤師・検査技師・看護師などのコメディカルスタッフ，データマネージャーなどである．実施される作業に対して標準業務手順書を定めており，一定の方法で遂行される．多様な作業が行われるが，研究責任医師は試験開始前にどのような業務を委受託するのか，範囲を明確にしておく．そして契約や覚書が交わされる．

研究実施中は，組織内のコミュニケーションに莫大な時間が必要となる．このようなコミュニケーションのうち，研究責任医師と各研究施設との連絡については，事務局機能を研究責任医師サイドに設置することが必要かもしれない．

それぞれの機能の概要は以下のようである．

表1 臨床研究支援センターの機能例

- 患者登録開始前
  - 研究計画書作成支援
  - 症例報告書作成支援
  - EDCシステム作成
  - 研究登録補助
- 患者登録・観察中
  - 患者登録・割付け
  - データマネージメント(データの品質管理・品質保証)
    - データ収集
    - 症例報告書からの入力
    - データの保管
    - 異常データの確認と問い合わせ
    - データベース固定
  - モニタリング
  - 一斉調査・中間解析準備
  - イベント判定資料の作成
- 観察終了後
  - 解析
  - 論文作成支援

a. 研究計画書作成支援

研究計画書は研究の設計図であり，研究の背景，目的，対象患者，介入方法，観察項目，必要対象患者数，予定される解析，研究組織，倫理的配慮，などの詳細が記載される．また同意文書，説明文書も含まれる．科学的に妥当であり，倫理的に問題のない研究計画書が緻密に作成されなければならない．研究計画書に基づいて各施設の倫理委員会が審査する．研究の途中で研究計画が変更される場合，多施設共同研究であれば，すべての施設で倫理委員会の再審査が必要になる可能性がある．このような変更が頻繁に起こらないように研究開始前の詳細な検討が必要である．

対象患者の選択過程には細心の注意が必要である．研究目的として想定した患者集団から，選択基準や除外基準を設けて適合する患者集団を決定し，更に実際に登録できる患者を集めなければならない．この過程で代表性が保たれているか否かが問題になり，想定した患者集団からの選択バイアスを生じない選択基準・除外基準を設定する必要がある．イベント判定，アウトカムの測定では，精密で妥当性のある測定が

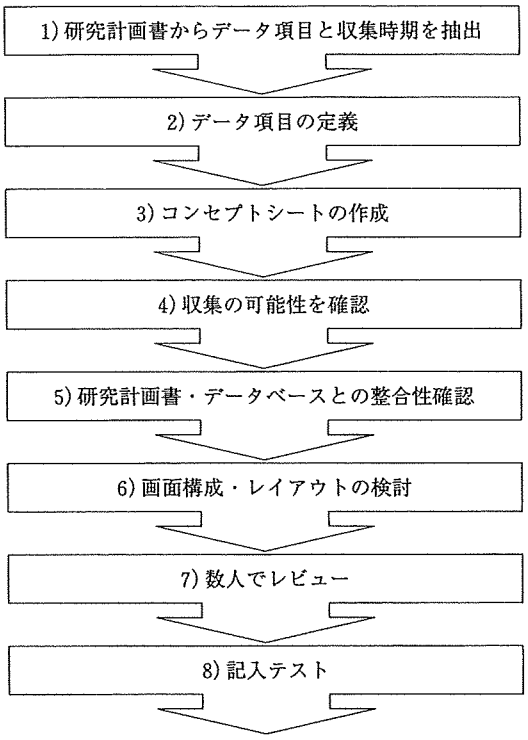

図2 症例報告書の作成手順

このような症例報告書の作成に臨床研究支援センターが寄与できる．7)のレビューは，数人で実施し単純ミスや思い込みを防ぐ．8)の記入テストは，数施設，実際に記入する人が実際のデータを用いて記入する．

行われるかが問題となる[2]．このような点の確認では，研究領域の専門医と研究デザインに通じる者の共同作業が必要になる．RCTであれば，ランダム化の手法や中間解析など専門性の高い統計処理が必要となる．生物統計家の関与が望ましい．

b. 症例報告書作成支援

症例報告書(case report form: CRF)は，データの信頼性に影響し，また入力作業の負担と関連する．結果的に患者登録にも影響する．作成される症例報告書は，研究計画書やデータベースと整合性がなければならない．簡潔・明瞭であり，記載者に誤解を生じさせないものが必要である．作成の手順は図2のようであり，取得データが多い場合，この作成は臨床医に負担である．このような症例報告書の作成過程に臨床研究支援センターが寄与できる．

c. Electronic data capturing(EDC)システム作成

データの取得方法として，近年EDCシステムが利用されることが多く，大規模な多施設共同研究に適している．EDCでは症例報告書からの転記が不要であり，転記に伴うエラーや字が読みにくいなどの問題が生じない．リアルタイムに研究の進捗を把握できるので，中央モニタリングを実施しやすい．大学病院医療情報ネットワーク(UMIN)などではINDICEというシステムを無料で提供している．しかしEDCでは，システム構築に時間が必要である．システムのバリデーションも負担のかかる過程である．また一度構築されたシステムを変更するのは必ずしも容易ではなく，大きな費用負担を伴うこともある．更にEDCを利用する場合，各施設や研究参加医師のID・パスワードを発行し，管理する必要がある．

d. 研究登録補助

2005年から介入を伴う前向きの臨床試験では，臨床試験の登録が求められるようになった．患者登録が開始される前に，UMIN-CTRやClinicalTrials.govなどの登録機関に登録されていなければ，優れた医学雑誌に研究結果を公表することはできない．

e. 患者登録・割付け

患者登録は電話やFAXでも可能だが，EDCであればweb上で行われる．割付けは，最小化法など動的割付けが利用できる．あらかじめ割付けのロジックを定めておき，システム上でこのような割付けを行うことが可能である．

f. データマネージメント

臨床研究支援センターの機能として重要なものに，データセンター機能がある．データセンターでは，データマネージメントを行い，データの品質管理・品質保証を行う[3,4]．EDCが利用されない場合は，症例報告書からダブルエントリーで入力し，データベースを作成していく．入手したデータに関して，欠損値や外れ値がないか，確認作業が実施される．EDCでは入力データの論理チェックがかけられるが，完全な論

理チェックの実装には無理がある．常に不十分と心得るべきであり，論理チェック範囲内でもエラーデータは存在する．エラーデータが疑われれば，担当医に問い合わせて(クエリ)正誤を確認する．必要があれば変更履歴を残しデータを修正する．データセンターではデータの保管に関して，組織的・人的・物理的・技術的安全管理措置がとられている．またデータのバックアップの体制がとられている．特に重要なアウトカムについてはデータの丁寧なクリーニングが実施される．その後，データベースが固定される．

g. モニタリング

臨床研究の遂行において，特に重要なのがモニタリングである．しばしば，研究参加医師が研究計画を厳密には把握していないことがある．このような場合，イベントを発生した患者の観察が中断されたり，規定外の治療がされたり，必要な検査が実施されなかったりする．治験では，モニターが施設を訪問し，研究計画書が遵守されているか調査される．また原資料の確認により，データの正確性も調査される．このような作業には莫大な費用がかかり，医師主導臨床研究で実施する経済的な余裕はない．現実的に品質を保証する方法は，中央モニタリングであろう．EDCでリアルタイムに集まるデータに基づいて，データセンターでモニタリングするものである．登録状況，検査データの入力状況，プロトコールの遵守状況，イベントや有害事象の発生状況，試験中止，エラーデータのクエリ応答状況，などがモニタリングされる．そしてモニタリングレポートが発行され，研究に参加する医師にフィードバックされる．また研究組織内の各種委員会(運営委員会，独立データモニタリング委員会，あるいはイベント判定委員会など)に報告される．この中央モニタリングに抜き取りに基づく監査が加わることが信頼性確保のために必要であろう．

h. 一斉調査・中間解析

研究の観察期間中に，一斉調査や中間解析が行われる場合がある．このような調査や解析の実施には周到な準備が必要である[5]．中間解析の実施や解釈には，極めて高度の統計学的な専門性が必要である．

i. 解　析

データベース固定後に解析が行われる．解析は研究責任医師の側で行う場合もあるが，臨床研究支援センターでも実施できる．

j. 論文作成支援

研究責任医師が論文を執筆するにあたっては，解析にかかわる事項だけでなく，CONSORTに準拠した論文の作成全般について支援できる．解析結果の解釈については，執筆者と解析者との意見交換が有用である．

3. JCRAC/臨床研究データセンターについて

JCRAC/臨床研究データセンターは，平成13年に厚生労働省のメディカル・フロンティア戦略(当時)のデータマネージメント事業として採択課題の研究者からの委託を受け，データマネージメントを支援する目的で設立された．財団法人日本公定書協会の事業とし，国立国際医療センター内にJCRAC委員会が組織され，データマネージメントの指導・助言にあたった．この間，検査技師や薬剤師がデータマネージャーとして臨床研究の支援活動に従事し，これに国立国際医療センターや東京大学の生物統計家，臨床疫学者，臨床医が加わっている．なお平成18年度からは，財団法人国際協力医学研究振興財団に移管されている．

これまで支援を行った研究は，循環器領域のRCT，国立病院機構EBM推進研究，自殺対策のための戦略研究，エイズ予防のための戦略研究など20研究を超え，RCTのほかに，コホート研究，横断的研究などの観察研究も含まれている．最大規模のRCTでは15,000人の登録と経過観察を実施中であり，今までの患者登録総計は約50,000人である．支援活動の内容としては，前項で記載した内容とほぼ一致しており，研究計画書作成支援，症例報告書作成支援，EDCシステム作成支援，ID・パスワード発行，患者登録・割付け，症例報告書からのデータ入力，データの確認・問い合わせ，中央モニタリ

ングとモニタリングレポートの発行，一斉調査の実施などである．また一部の研究では解析や調査結果報告書の作成を行った．

JCRAC/臨床研究データセンターは公的な臨床研究支援センターとして，治験と異なるタイプの臨床研究支援の経験を蓄積してきた．国内での臨床研究の推進のためには，更にデータマネージャーのキャリアパスの確立と教育機能の充実などが必要と考えられる．

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